HANDBOOK OF NUTRITION

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A Symposium

Prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association

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PREFACE

The Handbook of Nutrition is a symposium by leading authorities in the field of nutrition prepared under the auspices of the Council on Foods and Nutrition of the American Medical Association

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INTRODUCTION

Since the first edition of this Handbook was written, a World War has been fought and through the exigencies of this conflict great impetus has been given the study of nutrition Much new information has been gained The nutritive requirements of man under conditions seldom studied previously—in the desert, in the arctic in the jungle, at great altitudes in preparation for prolonged exertion after shipwreck and under many other conditions—became the subject of intensive investigation Added to the information thus acquired came the gains in knowledge which unhappily followed in the wake of the systematic starvation of races While these investigations did not always answer the questions asked they frequently threw revealing light on man's nutritive processes Much of this is included in the book

This period has been signalized by an increased interest in the production and composition of food and by a growing appreciation of good food Early evidence of this was seen in the promptness and well nigh universal enthusiasm with which enriched flour and bread were adopted The physician became more interested in nutrition and in the same measure the nutritionist became more interested in agriculture It has become evident that the eradication of nutritive failure throughout the world depends as much on agriculture as on education Dependence too is placed on the use of proper methods in the preservation and processing of foods The use of pharmaceutical products as short cuts to good nutrition have largely been discarded in favor of better food and physicians have come to agree with the investigators who have concluded that no gain in the fitness of adults can be accomplished by vitamin or other supplementation added to the good American diet

In time of war it became necessary more than ever to transport food great distances and to preserve it over long periods and this presented many problems What are the losses incident to the dehydration of foods? And what are the effects of these losses on the men who consume these foods? In other forms of processing what substances are preserved and what are

has made a complete about-face, and clinical opinion enthusiastically favors rather than frowns on a liberal protein allowance Evidence of this can be seen in the series of articles on Protein in Nutrition recently published under the auspices of the Council on Foods and Nutrition of the American Medical Association Protein has come into its own

Interest in vitamins, too, has taken a new turn It has been demonstrated that minor alterations in the structure of a vitamin may so completely reverse its physiologic activity as to change it from an essential nutrient into a metabolic antagonist Antivitamins do not usually occur in nature but through minor changes in structure new compounds are now being created which, as in the case of folic acid, have an effect directly opposed to that of the original substance and these compounds are being put to useful purposes By similar chemical substitutions a better understanding is being gained of enzymes and enzyme systems and the part these play in numberless nutritive processes New vistas are being opened in chemotherapy

Another promising field of study has been cleared by the discovery that a deficient diet will under appropriate conditions retard the development of certain diseases both neoplastic and infectious Witness for example the retardation of the formation of malignant tumors in experimental animals subjected to rigid restriction of caloric intake notably the failure under these circumstances of mammary tumors to develop in susceptible strains of mice Why do robust children (as is said to be the case) develop infantile paralysis more frequently than those who are ailing? And why the reported resistance to the virus of this disease exhibited by mice deficient in thiamin? This suggests a hitherto untried nutritional approach to the prevention of disease

Interest in the manner in which foods are offered to the public has not been permitted to lapse While intent on portraying to the physicians of America the constantly changing picture of the science of nutrition the Council on Foods and Nutrition has kept alive its original function of promoting accuracy in labeling and truthfulness in advertising The successful ad writer has great skill in fixing the reader s attention and the average housewife is probably more impressed by the advertisements that catch her eye than by the informative data that reach her through other channels

lost? In computing dietary values what is the difference in the total content and the available content of nutritive substances? What gives foods their taste appeal and why the difference in this respect in people? Some of these questions have been answered, others are awaiting solution

For the first time since Hippocrates as Elvehjem has recently remarked something approaching adequate attention is being given to nutrition in the treatment of disease This is seen not only in trends of scientific investigation but also in the routine treatment of patients at the bedside Witness the intensive search for antianemic substances and the alacrity with which the physician seizes upon each new substance as it is discovered Much of this interest has centered in protein Witness the dependence now placed upon protein in the treatment of patients who have been injured or who have undergone surgical operations, and the importance accorded this foodstuff in resistance to infection An even better illustration is seen in the adoption of the highprotein high vitamin diet in diseases of the liver, notably in infectious hepatitis and cirrhosis The results have been dramatic

This increased interest in protein began when Rose told of the dispensability and indispensability of certain amino acids and when, following this, animal experiments brought a much clearer understanding of the part these substances play in the human economy With this knowledge came the revelation that amino acid deficiency may develop even more rapidly than vitamin deficiency There has come too the new conception of amino acid imbalance This is based on the discovery that too wide a deviation from the optimum balance of amino acids fed in pure form to experimental animals may so upset physiologic processes as to do actual harm and has led to the somewhat novel suggestion that a smaller intake of good protein supplying amino acids in proper proportion is more wholesome than a more liberal ration of poor quality The development of protein hydrolysates and the facility thus accorded the physician for giving amino acids intravenously has stimulated still further interest in this foodstuff Only a few years ago a host of ills were ascribed to protein decomposition products and anything approaching liberality in protein intake was believed to be distinctly harmful All of this is now changed The physician

Part I

INDIVIDUAL NUTRIENTS

so much so that the most potent influence today in making the American people food conscious is said to be the paid advertisements of food manufacturers The Council realizes this and believes that it has seen gratifying results in its efforts to guide food advertising along the right channels It has been encouraged not only by the interest of the consumer but also by the fine cooperation of industry

Countless ages ago man was differentiated from his anthropoid ancestors by evolutionary processes in which, if we believe Darwin dominance was accorded those physiologic variants most suited to the environment In time these variants became fixed and grew to be characteristic of the newly developed species Although this differentiation took place in an evolutionary process in which man fitted himself to the available diet, it is subject to philosophic discussion as to whether this diet was ideal Would a different diet have led to progress upward in a different and more advantageous direction? And would the better values thus encompassed have been physical or spiritual?

Later there came a change and man became less subject to the grim hand of fate As he acquired the arts of civilization he learned to protect himself from his natural enemies and was able thereby largely to circumvent the further immediate action of natural selection But this also brought disadvantages I shall not insist upon listing among these disadvantages the possible effect upon the race of the multiplication of the unfit and the protection of the weakling, I should like to emphasize rather the changes which civilization had produced in the character of man s natural diet and the implications which these changes may have for his future development Improved agriculture the domestication of animals the processing and refinement of foods and many other factors have altered the diet to which man became adjusted through the ages and have provided today attractive readily available foods which the carefully protected, nervously unstable twentieth century man, constantly subject to emotional bombardments on every side, prefers and willingly consumes Can we through the study of present day nutritional environment take a hand in evolution and learn so to control man s nutritive processes as to make it possible for him the better to fulfill his destiny? This I take it, is an ultimate object of this handbook

James S McLester

CHAPTER I

PROTEINS IN NUTRITION

HOWARD B LEWIS

The term protein was suggested by the Dutch chemist Mulder in 1839 as a designation for the universal component of tissues, both plant and animal Protein was characterized by him as "unquestionably the most important of all known substances in the organic kingdom Without it no life appears possible on our planet Through its means the chief phenomena of life are produced "[1] Today, more than a century after Mulder the proteins are still 'first' (Greek, *prōteios)* in the regulation of vital processes and disturbances in their metabolism are associated with nutritive failure and with many pathologic conditions with which the physician is confronted.

Proteins are normal constituents of all animal cells and body fluids with the exception of the bile and the urine They are essential components of both the protoplasm and the nucleus of the cell, hence they exert a profound influence on growth They are important in the regulation of osmotic relations between cells and intercellular fluids and between tissues and blood and play a significant role in the fluid balance of the body Many of the best characterized enzymes have been obtained in crystalline form and have the properties of proteins (the 'protein enzymes)[2] A considerable number of the hormones chemical regulators of the body either are proteins (the so called protein hormones)[3] or are derivatives of proteins Many of the substances associated with immunologic and antigenic reactions and similar phenomena are known to be proteins In recent years the causative agents of certain

1 Mulder G J The Chemistry of Animal and Vegetable Physiology cited by Mendel, L. B Nutrition The Chemistry of Life New Haven Conn Yale University Press, 1923 p 16

2 Northrop J J Crystalline Enzymes, New York Columbia University Press 1939

3 White A Protein Hormones in Cold Spring Harbor Symposia on Quantitative Biology Cold Spring Harbor L. I N Y The Biological Laboratory 1938 vol 6 p 26.

The large molecules of even the simpler proteins may be compared with those of some other important constituents of tissues or body fluids sodium chloride, 58, urea 60, ascorbic acid, 176, dextrose 180, lactose, 342, carotene (provitamin A), 537, and glyceryl tristearate (a typical fat), 891

When this large protein *molecule is broken down by* the addition of the elements of water (hydrolysis), a considerable number of much simpler units or building stones are formed whose molecular weights range from 75 (aminoacetic acid known also as glycocoll or glycine) to 240 (cystine) These units have the structure and properties of ampholytes (dissociation so that they may function either as an acid or as a base depending on the p_H of the environment) and are known as α amino acids From the chemical standpoint they are characterized by the presence of a carboxyl (COOH) group with acidic properties and an amino (NH_2) group with

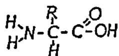


Fig 1—Structure of an amino acid

basic properties the two groups being attached to the same carbon atom

The character of the remainder of the amino acid molecule (designated by R fig 1) varies but all the typical products of hydrolysis have in common the presence of the carboxyl and amino groups Important chemical groupings in various amino acids are sulfur (cystine and methionine), hydroxyl (threonine and serine), benzene nucleus (phenylalanine and tyrosine), guanidine nucleus (arginine), indolyl ring (tryptophan) and imidazolyl ring (histidine)

Certain units or amino acids present in the protein molecule are considered of especial importance in the structure of tissue (growth) and are commonly designated as the essential amino acids The chemical nature of these essential units will be discussed subsequently The formulas of the other amino acids may be obtained from any of the numerous standard textbooks on biologic chemistry

The amino acids are joined to each other in the protein molecule by a linkage known as the peptide linkage

virus diseases (notably the tobacco mosaic and the bushy stunt of the tomato) have been obtained in crystalline form and exhibit the characteristic properties of nucleoproteins, yet when inoculated into the proper host they multiply and give rise to the specific pathologic changes associated with the virus[4] Bacteriophage a filtrable agent with the properties of a virus is also believed to be a nucleoprotein Finally, a nucleoprotein is the major constituent of cell nuclei and is believed to constitute the chromatin of the nucleus and thus to form the principal component of the chromosome[5]

TABLE 1—*Sources and Approximate Molecular Weights of Proteins*

Protein	Source	Estimated Molecular Weight
Insulin	Pancreas	35 000 or 46 000
P psin	Gastric juice	35 900
Bence-Jones protein	Urine	[illegible]
β Lactoglobulin	Milk	42 000
Ovalbumin	Hen s egg	43 000
Zein	Corn	50 000
Hemoglobin	Human blood	70 000
Serum albumin	Human blood	70 000
γ Globulin	Human blood	156 000
Urea e	Jack bean	42[illegible] 000
Thyroglobulin	Thyroid	650 000
Antipneumococcus serum globulin..	Horse blood	845 000
Bushy stunt virus	Tomato plant	7 600 000
Tobacco mosaic virus	Tobacco plant	40 000 000

It is notable that proteins exist as large molecules or possibly aggregates of molecules In table 1 are presented the estimated molecular weights of a few important proteins It should be pointed out that in the determination of the molecular weights of proteins many difficult problems arise and that the values obtained by the various methods do not check exactly The values presented will it is believed afford some approximation of the probable size of protein molecules

4 Stanley W M Some Chemical Medical and Philosophical Aspects of Viruses Science 93:145 151 (Feb 14) 1941

5 Mirsky A E Chromosomes and Nucleoproteins in Nord F F and Werkman C H Advances in Enzymology and Related Subjects of Biochemistry New York Interscience Publishers Inc 1943 vol 3 p 1 Darlington C D Nucleic Acid and the Chromosomes in Symposia of the Society for Experimental Biology London Cambridge University Press 1947 vol 1 p 252

6 Omitted

When two amino acids are joined in peptide linkage, two different peptides may be obtained, with three amino acids six peptides and with five amino acids, 120 peptides These are known as isomers, since they are all made up of the same units and have the same percentage composition They differ, however in the arrangement of the amino acids in the peptide chain (for instance in the case of a tripeptide, a-b-c a c-b, b a c, b c a c a b and c-b a, when a, b and c are three different amino acids) Since more than twenty amino acids are known to be of general occurrence in the protein molecule it is obvious that the possible number of isomeric proteins (polypeptides) is very large A peptide made up of twenty amino acids most commonly obtained in the hydrolysis of protein[7] each acid occurring once only in the chain would have a molecular weight of about 2 700 A simple calculation shows that the number of possible isomers of this peptide would be 2 432 902 008 176 640 000 a number beyond the range of human thought[8] Each of these peptides would have the same percentage composition would yield the same amino acids on hydrolysis in the same proportions and would have similar properties Each would differ from the other in some slight variation in the arrangement of the component amino acids of the peptide chain Each would therefore be a chemical individual distinct from the other isomeric peptides

If it is remembered that the protein molecule is much larger than the peptide just discussed that native proteins vary greatly in the amounts of amino acids which they yield on hydrolysis and that some linkages other than the simple peptide linkage almost certainly occur in the protein molecule, it is evident that the possible number of different proteins as they exist in nature is almost infinite This individuality of natural proteins finds expression in the so called specificity of the proteins This may be most simply defined by the statement that every species tends to construct within the organism a protein characteristic of that species Thus casein of cow's milk is believed to differ from casein of goat s milk protein of beef muscle to differ from protein of pork muscle and serum protein of human

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7 Two amino acids commonly listed in textbooks of biochemistry are not now accepted as units of the protein molecule i. e hydroxy glutamic acid and norleucine

8 Abderhalden E. Lehrbuch der physiologischen Chemie ed. 6 Berlin Urban & Schwarzenberg 1931 p 30

in which the basic (amino) group of one acid is linked to the acidic (carboxyl) group of the adjacent acid with the loss of a molecule of water A compound made up of two acids thus joined is known as a dipeptide (fig 2), and a similar compound which contains several (usually an unknown number) amino acids bound together in the peptide linkage is known as a poly peptide

Hydrolysis of the dipeptide for which the formula is given would break the peptide linkage (-NH-CO-), and the component amino acids would be obtained While the peptide linkage may not be the only linkage between the amino acids of the protein molecule, it is certainly by far the most important one This is borne out by the chemical properties of native proteins (pro-

Fig 2—Structure of a dipeptide

teins as they are found in nature as contrasted with derivatives formed by the action of heat alcohol water salts, enzymes and the like) The biologic reactions of the proteins are also more closely related to those of amino acids than to those of any other type of hydrolytic product of protein such as proteoses or peptones

Just like the amino acids, which are ampholytes and may react with either acids or bases depending on the p_H of their environment, the proteins as complexes of amino acids (polypeptides) may combine with either acids or bases For the most part the proteins as they exist in fluids and tissues of the animal organism func tion as acids (play the role of anions) and are in com bination with bases (cations) Thus the protein hemo globin of the erythrocytes is combined in the cell with base (chiefly potassium) as a salt similarly milk contains various salts of casein, of which calcium caseinate is important

When two amino acids are joined in peptide linkage, two different peptides may be obtained, with three amino acids, six peptides, and with five amino acids 120 peptides These are known as isomers, since they are all made up of the same units and have the same percentage composition They differ however in the arrangement of the amino acids in the peptide chain (for instance in the case of a tripeptide, a b-c a-c b b a-c b c a c-a b and c b a when a, b and c are three different amino acids) Since more than twenty amino acids are known to be of general occurrence in the protein molecule, it is obvious that the possible number of isomeric proteins (polypeptides) is very large A peptide made up of twenty amino acids most commonly obtained in the hydrolysis of protein,[7] each acid occurring once only in the chain, would have a molecular weight of about 2 700 A simple calculation shows that the number of possible isomers of this peptide would be 2 432 902 008 176 640 000 a number beyond the range of human thought[8] Each of these peptides would have the same percentage composition would yield the same amino acids on hydrolysis in the same proportions and would have similar properties Each would differ from the other in some slight variation in the arrangement of the component amino acids of the peptide chain Each would therefore be a chemical individual distinct from the other isomeric peptides

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[8] Abderhalden E Lehrbuch der physiologischen Chemie ed. 6 Berlin Urban & Schwarzenberg 1931 p 302

sive observations have been reported with egg white[12] These observations are of special significance in relation to the phenomena of sensitization to specific protein foods However, it should be remembered that the methods of immunology are capable of detecting exceedingly minute amounts of protein and that the total amount of protein absorbed thus unaltered must be slight One may then, with a reasonable degree of confidence look to the behavior of the individual amino acids for the interpretation of the role of protein in normal nutrition

The products of the digestion of proteins, chiefly the amino acids enter the portal blood on absorption from the intestine and are distributed to the tissues by the systemic blood The postabsorptive increase in the amino acid nitrogen of the blood, although not large is unquestioned The amino acids are rapidly taken up by the tissues, and the amino acid content of the blood returns to normal[13]

One of three fates awaits the amino acids which thus enter the cell The first is condensation with other amino acids selected by the particular tissue in question from the pabulum supplied to it by the blood to form the protein characteristic of that particular tissue or cell This specific synthesis, the converse of digestion, makes possible the maintenance of the individuality of the cell This process acquires a particular significance in young animals in which building of new tissues, growth, must occur for normal development and in the adult in normal pregnancy and lactation

A second metabolic path is utilization of the amino acids for some special purpose in the animal economy apart from the general synthesis of cellular protein Examples of this are the synthesis of such proteins as hemoglobin fibrinogen and the serum proteins Amino acids are utilized also for the formation of specific proteins with hormonal function (insulin and prolactin) or amino acid derivatives which are hormones (epinephrine and thyroxine) or chemical re ulators which

12 Wilson S J and Walzer M Abso ption of Und ge ted Proteins in Human Beings IV Absorption of Unaltered Egg P teins in Infants and Children Am J D s Ch ld **50** 49 54 (July) 1935 Ratner B and Gruehl H L Passage of Native Frot ins Th ough the Normal Gastrointestinal Wall J Clin Inve t gat on **13** 517 53? (July) 1934

13 Van Slyke D D Phys ology of the Amino Acids Science **95** 259 263 (Ma ch 13) 1942

are not usually classed as hormones (glutathione histamine and creatine) The synthesis of the 'protein enzymes" (pepsin trypsin, catalase and carbonic anhydrase) also occurs The details of the reactions which lead to the synthesis of such specialized proteins and protein derivatives are not as yet clearly understood

After the needs of the cells for these two purposes have been met, an excess of amino acids may still remain in the cells The fate of this amino acid fraction is deamination—removal of the nitrogenous portion of the molecule—and utilization of the non nitrogenous portion, since in contrast to fat and carbohydrate, storage of protein or amino acids for any considerable time does not appear to be possible The nitrogenous fraction of the molecule, split off as ammonia is rapidly converted into urea under normal conditions and is eliminated in this form by the kidneys The efficiency of this transformation is demonstrated by the fact that normally systemic blood contains less than 0 1 mg of ammonia nitrogen per hundred cubic centimeters while the urea content of normal blood calculated as urea nitrogen is approximately 17 mg per hundred cubic centimeters The non nitrogenous residue which remains after deamination may either be transformed into dextrose and used in this form the antiketogenic fraction of the protein molecule or be converted to fatty acids the ketogenic fraction of the protein molecule Whether the non nitrogenous residue is converted to dextrose for utilization in that form depends on the chemical structure of the original amino acid In general one may say that about half of the amino acids present in the molecule of any individual protein may give rise to dextrose in intermediary metabolism

Physiologic and nutritional studies alike have emphasized the role of the amino acids as structural elements, the building stones of living protoplasm What are the amino acid requirements for the construction of new cells? Are all the amino acids of equal importance in nutrition? These questions have been answered in part by the studies of Rose which were based on the pioneer work of Hopkins and of Osborne and Mendel It should be emphasized that the discussion immediately following concerns the requirements for

growth of one species, the white rat Rose[14] first demonstrated that it was possible to obtain normal growth of young white rats when the protein element of the diet was supplied by a mixture of chemically pure amino acids, which included those acids known to be of general occurrence in the protein molecule The effect of the removal of the various individual amino acids from this mixture was then studied The absence of certain acids from the diet resulted in impaired growth or in some cases considerable losses in weight and ultimately death These amino acids designated as essential could not be synthesized by the rat and had to be supplied in the diet in adequate amounts or

TABLE 2—*The Amino Acids Essential for Growth of the White Rat*

Amino Acid	Characteristic Chemical Grouping
Threonine	Hydroxy group on 4 carbon chain
Valine	5 carbon branched chain
Leucine	6 carbon branched chain
Isoleucine	6 carbon branched chain
Lysine	° amino groups on 6 carbon chain
Tryptophan	Indole nucleus
Phenylalanine	Benzene nucleus
Methionine	Methyl thiol group
Histidine	Imidazole nucleus
Arginine	Guanido group

Arginine has a special position as discussed in the text

nutritive failure resulted The withdrawal of other amino acids did not influence the rate of growth These amino acids the nonessential amino acids must therefore be synthesized in the body at a speed commensurate with the needs for normal growth In table 2 is presented Rose's listing of the amino acids on this basis In further studies in which rats have been fed a mixture of the ten essential amino acids listed with the omission of all the nonessential acids this mixture of amino acids in suitable proportions has been observed to be a 'remarkably efficient source of nitrogen for many physiologic functions[15] On such mixtures,

14 Rose W C Th Significance of the Amino Acids in Nutrition in Harvey Lectures 1934 1935 Baltimore Williams & Wilkins Company 1936 vol 30 p 49 The Physiology of Amino Acid Metabolism Proc, Inst Med Chicago 12 93-110 (April 15) 1938

15 (a) Rose W C Amino Acid Requirements of Man Fed Proc 8:546 557 (Jun) 1949 (b) Harte R A and Travers J J Human Amino Acid Requirements Science 105 15 16 (Jan 3) 1947

rats not only grew satisfactorily but were able to reproduce and rear their young which is evidence of effective lactation In the group of essential amino acids arginine occupies a unique position Growth is possible in the absence of this amino acid from the diet but the rate of growth is distinctly less than when arginine is supplied Rose has defined an indispensable dietary component as 'one which cannot be synthesized by the animal organism, out of the materials ordinarily available at a speed commensurate with the demands for normal growth'[16] If this definition is accepted arginine is classed as essential This classification of amino acids is one based on the growth requirements of rats Whether modifications must be made when requirements for pregnancy lactation or maintenance are under consideration remains to be determined

The possibility of species differences must also be considered It is known that all of the amino acids essential for the young white rat are also essential for the growth of the young chick[17] The amino acids required for maintenance of nitrogen balance in young adult humans has been studied by Rose[15] and Holt.[18] According to Rose all of the amino acids essential for the growth of the young white rat except histidine and arginine are necessary as dietary constituents if nitrogen balance is to be maintained in human adults When any one of the eight essential amino acids was excluded from the food there resulted a 'pronounced negative nitrogen balance a profound failure in appetite a sensation of extreme fatigue and a marked increase in nervous irritability These symptoms were observed even when the subjects were unaware that a dietary alteration had been made. With the return of the missing amino acid to the food nitrogen equilibrium was reestablished promptly and the subjective symptoms disappeared'[15a] Histidine and arginine on the other hand were not necessary for the maintenance of nitrogen equilibrium in the human adult.

Rose[15a] has gone further and has attempted to estimate the daily requirements of the essential amino

16 Rose W C The Nutritive Significance of the Amino Acids, Physiol Rev 18: 109 136 (Jan) 1938
17 Almquist H J Evaluation of Amino Acid Requirements by Observations on the Chick J Nutrition 34: 543-563 (Nov) 1947
18 Holt L. E Jr Amino Acid Deficiencies in Man in Nutrition and Public Health in the Postwar Period Detroit, Children's Fund of Michigan 1944 p 193

acids in human beings under the previously outlined conditions These values (table 3) represent the minimal and recommended intakes of a man weighing 70 Kg It will be noted that the weight of the amino acids represented in the table totals slightly over 13 Gm Full details of these experiments will be awaited with much interest

In the experiments of Holt[18] with young men, an interesting observation was the decrease in the number of spermatazoa in the seminal plasma when arginine was removed from the diet and the return to normal counts when arginine was restored to the diet These

TABLE 3—*Minimum and Recommended Intakes for Normal Man When Diet Furnishes Sufficient Nitrogen for Synthesis of Nonessential*[18a] *(Strictly Tentative Values)*

Amino Acid	Minimum Daily Requirement Gm	Recommended Daily Intake Gm	Subjects Tested No
L-Tryptophan	0 25	0 5	31[1]
L-Phenylalanine	1 10	2.2	22
L-Lysine	0 80	1 6	27
L-Threonine	0 50	1 0	19
L-Valine	0 80	1 6	23
L-Methionine	1 10	.2	13
L-Leucine	1 10	2 2	8
L-Isoleucine	0 70	1 4	8

1 All of th se subjects have been kept in balance on 0 3 Gm. or less

experiments must be confirmed and extended before practical applications in the clinical treatment of sterility in men are attempted It is known that the testicular tissue of fish has a high content of arginine but so far as is known to me no analysis for arginine has been made with human spermatazoa nor have similar analyses of other mammalian sperm been available Recently however analysis of bovine sperm has revealed a high arginine content (25 47 per cent on a fat-free moisture-free and ash free basis)[19]

It is assumed that the amino acids not listed in table 2 are dispensable and, if absent from the diet can be synthesized Womack and Rose have discussed the

19 Sarkar B C R Luecke R W and Duncan C W The Amino Acid compos tion of Bovine Sperm, J Biol Chem. 71 463-465 (Dec) 1947

interrelationships of arginine proline and glutamic acid in the diet[20] Glutamic acid is tentatively listed as non essential for growth of the young white rat

The tissue protein synthesized during growth in such experiments must be assumed to be of a type normal and characteristic of the species since it is considered axiomatic that "the tissues either form a typical protoplasmic product, or none at all"[21] In the case of the sulfur containing amino acids the evidence seems clear that the dispensable cystine may be synthesized from the essential methionine[2]

The function of the essential amino acids other than for the construction of new protoplasm is not entirely clear Methionine is a precursor of cystine an amino acid important in the molecule of the proteins of epidermal structures and also of certain hormones particularly insulin in the molecule of which 12 per cent of cystine is present and no methionine[23] Methionine also supplies methyl groups for the synthesis of choline, a dietary essential and of creatine important for maintenance of muscle function[24] Phenylalanine presumably furnishes the nucleus for the synthesis of thyroxine the iodine-containing amino acid present in the specialized physiologically active thyroglobulin of the thyroid, and of epinephrine, the endocrine principle of the adrenal medulla[5] Histidine may be decarboxylated to yield histamine the amine whose biologic role seems demonstrated[26] Arginine is believed to supply the amidine group for the synthesis of creatine[7] Specific

20 Womack M and Rose W C. The Role of Proline Hydroxyproline and Glutamic Acid in the Diet, J Biol. Chem **171** 37 50 (Nov) 1947

21 Osborne, T B and Mendel L. B Amino Acids in Nutrition and Growth, J Biol. Chem. **17**: 325 349 1914

22 Lewis H B The Significance of the Sulfur *Containing* Amino Acids in Metabolism in Harvey Lectures 1940-1941 Baltimore Williams & Wilkins Company 1942 vol 36 p 159 Rose W C and Wood T R The Synthesis of Cystine in Vivo J Biol Chem **141** 381 389 (Nov) 1941

23 Miller G L and du Vigneaud, V The Cystine Content of Insulin, J Biol Chem **118**: 101 110 (March) 1937 du Vigneaud, V Miller G L. and Rodden C. J On the Question of the Presence of Methionine in Insulin ibid **131**: 631 640 (Dec) 1939

24 du Vigneaud V The Significance of Labile Methyl Groups in the Diet and Their Relation to Transmethylation in Harvey Lectures 1942 1943 Baltimore Williams & Wilkins Company 1944 vol 38 p 39 Lewis[22]

25 Gurin S and Delluva, A M The Biological Synthesis of Radioactive Adrenalin from Phenylalanine J Biol. Chem. **170** 545 550 (Oct.) 1947

26 Best, C. H and McHenry E W Histamine Physiol Rev **11** 371-477 (Oct) 1931

27 Bloch, K and Schoenheimer R The Biological Precursors of Creatinine, J Biol Chem. **138**: 167 194 (March) 1941

functions for the other essential amino acids are yet to be suggested It is also of interest to note that the essential amino acids comprise slightly more than half of the amino acid rests of β lactoglobulin, one of the best characterized purified proteins [28]

An interesting recent development has been relationships between vitamins and amino acids It was observed that in rats fed certain types of low protein diets retarded growth resulted a retardation which could be corrected by the addition of either nicotinic acid or tryptophan to the diet This suggested that tryptophan might function as a biologic precursor of nicotinic acid [9] When rats or mice were fed diets deficient in pyridoxine an abnormal chromogenic substance, xanthurenic acid which was shown to be a derivative of tryptophan, was excreted in the urine [30] Administration of tryptophan increased the excretion of xanthurenic acid The full significance of these studies is not clear, but it appears probable that study may reveal more such relationships between proteins (amino acids) and the various vitamins [31]

For the proper utilization of the observations concerning the essential and nonessential amino acids and their role in the diet more complete information is needed concerning the amino acid composition of important food stuffs on which our supply of dietary protein depends The nutritive value of important protein foods can then be evaluated Some data of this type in which the newer microbiologic methods are used as well as chemical methods are now available [32] An

28 Brand E Sa del L J Goldwater W H Kass N B and Ryan F J The Empirical Formula of β Lactoglobulin J Am. Chem Soc **67:** 1524 1537 (Sept) 1945

29 Krehl W A Henderson L M de la Huerga J and Elvehjem C A Relation of Amino Acid Unbalance to Niacin—Tryptophan Deficiency in Growing Rats J Biol Chem **166** 531 540 (Dec) 1946 Schweigert B S and Pearson P B Effect of Vitamin B Deficiency on the Ability of Rats and Mice to Convert Tryptophan to N Methylnicotin Amide and Nicotinic Acid ibid **168:** 555 561 (May) 1947 Singal S A Sydenstricker V P and Littlejohn J M The Effects of Some Amino Acids on the Growth and Nicotinic Acid Storage of Rats on Low Casein Diets ibid **171:** 203 207 (Nov) 1947

30 Lepkovsky S Roboz E and Haagen Smit A J Xanthurenic Acid and Its Role in the Tryptophane Metabolism of Pyridoxine Deficient Rats J Biol Chem **149:** 195 201 (July) 1943 Miller E C and Baumann C A Relative Effects of Casein and Tryptophane on the Health and Xanthurenic Acid Excretion of Pyridoxine Deficient Mice ibid **157** 551 567 (Feb) 1945

31 Mitchell H H The Chemical and Physiological Relationships Between Vitamins and Amino Acids in Harris R S and Thimann K V Vitamins & Hormones New York Academic Press Inc 1943 vol 1 pp 157 194

32 Block R J and Mitchell H H The Correlation of the Amino Acid Composition of Proteins with Their Nutritive Value Nutrition Abstr & Rev **16:** 249 278 (Oct.) 1946

important application of the observations that properly chosen mixtures of amino acids may replace proteins in nutrition has been the clinical use of protein hydrolysates prepared for the most part by enzymatic action on proteins in vitro These preparations may be administered either orally or parenterally The utilization of intravenously injected amino acids over a considerable period was first demonstrated by Henriques and Anderson[33] in experiments with a goat

The clinical use of such protein hydrolysates has been studied extensively by Elman[34] and others[35] Intravenous administration of protein hydrolysates has been shown to be beneficial when feeding by mouth is not possible or is inadvisable Since hydrolysis destroys the biologic specificity of the native proteins protein hydrolysates orally administered have proved of value in supplying nitrogen to persons with severe food allergies Whipple and his co workers have demonstrated that protein hydrolysates may function effectively in the restoration of plasma protein in dogs in which reserve of tissue and plasma proteins have been depleted by bleeding[35d] More extensive clinical studies of the usefulness of protein hydrolysates in medical and surgical patients are desirable

The problem of the amount of protein which is essential or optimal in the diet of human beings has received much attention The optimal protein level is particularly important in view of the higher cost of protein foodstuffs notably meat which makes it of doubtful economy to use protein primarily for energy purposes

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33 Henriques V., and Anderson A C. Ueber parenterale Ernahrung durch intravenose Injektion Ztschr f physiol Chem **88** 357 369 1913

34 Elman, R Parenteral Alimentation in Surgery with Especial Reference to Proteins and Amino Acids New York Paul B Hoeber Inc 1947

35 (*a*) Allison J B Anderson J A and Seeley R. D The Determination of the Nitrogen Balance Index in Normal and Hypoproteinemic Dogs Ann New Yo k Acad. Sc. **47** 245 ?71 (Oct 30) 1946 (*b*) Barnes H and Bosshardt D K The Evaluation of Protein Quality in the Normal Animal ibid **47** 273-?96 (Oct 30) 1946 (*c*) Chow B F The Electrophoretic Studies on the Effect of Protein Depletion on Plasma Proteins and the Regeneration of Plasma Proteins After Oral Admin stration of Hydrolysates Prepared from Casein and Lactabumin, ib d. **47**: 297 316 (Oct. 30) 1946 (*d*) Whipple G H Robscheit Robbins F S and Miller L. L. Blood Protein Regeneration and Interrelation ibid 317 3 6 (*e*) Peters J P Nitrogen Metabolism in Acute and Chronic Disease ibid **47** 3?7 345 (Oct. 30) 1946 (*f*) Elman R The Intravenous Use of Protein and Protein Hydrolysates, ibid. **47**: 345 357 (Oct. 30) 1946 (*g*) Co Tui Clinical Experience with Oral Use of Protein Hydrolysates, ib d **47**: 359 373 (Oct 30) 1946 (*h*) Cannon P R. Amino Acid Utilization in the Surgical Patient, J A. M A **135**: 1043 1046 (Dec. 20) 1947

Stare[36] recently stated that, for the production of 1,000,000 human food calories derived from cane sugar, 0 15 acre of land is required, this is in sharp contrast to 17 acres the acreage required to produce the same amount of energy from steers

It is usually accepted that luxus consumption of protein over prolonged periods is of no permanent value to the adult organism since, in contrast to fat and carbohydrate protein and its building stones the amino acids are not stored[37] This is seen in the state of nitrogenous equilibrium or balance If the dietary protein of a normal adult is adequate the nitrogen of the diet (chiefly protein nitrogen) is equal to the nitrogen of the excreta (mainly the nitrogen of the urine) If to the diet of such a person increased amounts of protein are added there is a sharp increase in the nitrogenous waste products of the urine (largely urea derived from protein catabolism) and within a relatively short time nitrogenous equilibrium is again obtained but at a higher level of excretion If new protein is being synthesized in the body (growth pregnancy and lactation) the nitrogen excreted is less than that of the diet and the subject is said to be in positive nitrogen balance When the nitrogen excreted is greater than the dietary nitrogen a condition of negative balance is obtained This indicates an inadequate intake of dietary protein or an excessive breakdown of body protein associated with disease

The level of endogenous nitrogen protein metabolism may be obtained by a consideration of the nitrogen excretion of an adult maintained on a diet high in its content of fat and carbohydrate but containing no protein Experimentally this has been observed to approximate 3 Gm a day for a man weighing 70 Kg or about 20 Gm of protein[38] There is however, evidence that to provide a safe allowance for health protein in excess of the requirements for maintenance is essential It is argued that excessive consumption of protein imposes a burden on the organism and is likely to be harmful The proponents of the high protein diet on

36 Stare, F J Fiasco in Food Atlantic Monthly **181** 21 22 (Jan) 1948

37 Kosterlitz H W The Storage of P otein in the Adult An mal Nutrition Abstr & Rev **15** 1 14 (July) 1945

38 Martin C J and Robinson R. The M nimum N t ogen Expenditure of Man and the Biologic Value of the Var ous Proteins for Human Nutrition J B ochem **16** 407-447 (June) 1922

the other hand argue that a surplus of protein may have a beneficial effect on health and well being and cite studies of racial groups which indicate that physical efficiency and health can be related directly to the intake of protein and particularly of animal protein The high protein diet of the Eskimo in which the protein is obtained almost entirely from meat does not appear to have resulted in a high incidence of renal disease in this group[39] The carefully made studies of the metabolism of two Arctic explorers who lived for a year in the temperate zone on a diet of meat only are of particular interest It must be remembered however that in studies of human populations the protein element is only one of many factors in health and that it is difficult to assess the role of dietary protein alone without many greatly extended studies[40]

Outstanding among the pathologic conditions which have been associated with prolonged ingestion of a diet inadequate in its protein content is nutritional edema (known also as war or starvation edema) which has been observed clinically in Europe in the Orient and in the United States and can be produced experimentally in animals maintained on a low protein diet[41] The continued ingestion of the low protein diet results in low levels of plasma protein (particularly the albumin fraction) and the resultant lowering of the effective osmotic pressure of the plasma is believed to be one of the causes of the edema.

This discussion indicates the desirability of caution in the selection of a standard protein level for national nutrition It is not necessary to enter into the details of the controversy between the advocates of the low and high protein diet a controversy which is excellently and impartially presented in the classic text of Lusk[42] Sherman after a careful consideration of the acceptable balance experiments with human beings in which nitro-

39 McClellan W S and Du Bois E. F Clinical Calorimetry XLV Prolonged Meat Diets with a Study of Kidney Function and Ketosis, J Biol Chem 87:651 668 (July) 1930 McClellan W S Rupp V R. and Toscani V XLVI Prolonged Meat Diets with a Study of the Metabolism of Nitrogen Calcium and Phosphorus ibid. 87:669-680 (July) 1930

40 Cuthbertson, D P Quality and Quantity of Protein in Relation to Human Health and Disease, Nutrition Abstr & Rev 10 1 20 (July) 1940

41 Youmans J B Nutritional Deficiencies Diagnosis and Treatment, Philadelphia, J B Lippincott Company 1941

42 Lusk, G The Elements of the Science of Nutrition, ed. 4 Philadelphia, W B Saunders Company 1928 p 448.

gen equilibrium was established at low levels of dietary protein concluded that "a standard allowance of 1 Gm of protein per kilo of body weight per day appears, therefore, to provide a margin of safety of 50 to 100 per cent as far as requirements of adult maintenance are concerned "[43] This standard for adult maintenance has been accepted almost universally while the need for larger amounts of protein in diets of growing children and of pregnant and lactating women is clearly recognized The recently adopted standards for national nutrition, as proposed by the Food and Nutrition Board of the National Research Council provide for 70 Gm of protein a day in the diet of a man weighing 70 Kg and 60 Gm of dietary protein for a woman weighing 56 Kg[44]

Estimates of the increased requirements for protein during pregnancy and lactation vary greatly[45] The protein requirement per kilogram of body weight is high in infancy and decreases as growth occurs until after puberty when the adult requirements only are necessary The desirable amount of dietary protein is estimated to vary from 4 Gm per kilogram a day at 1 to 3 years to 2 Gm at 17 to 18 years[44] The necessity of proteins of milk during the period of active growth can hardly be overemphasized That increased muscular activity necessitates a larger intake of protein is as yet unproved Traditionally the diet of highly trained athletes and of laborers engaged in hard work whose calorific requirements are high, contains much meat and supplies large amounts of proteins[40]

An increased destruction of tissue protein has long been recognized in a variety of infectious diseases More recently loss of nitrogen as evidenced by decided negative balances has been observed in patients undergoing surgical treatment (notably after fractures) and in patients with severe burns[46] In an attempt to make good this loss of protein from the body a loss which may continue for some days high protein diets have

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43 Sherman H C Gillett L H and Osterberg E Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein J Biol Chem **41** 97 109 (Jan) 1920

44 Recommended Dietary Allowances Revised 1948 Bulletin 129 Food and Nutrition Board National Research Council October 1948

45 Footnote 44 Garry R C, and Wood H O Dietary Requirements in Human Pregnancy and Lactation A Review of Recent Work Nutrition Abstr & Rev **15**: *591 6 1 (April) 1946*

46 Elman[34] Peters J P Problems of Nitrogen Metabolism, Federation Proc **3** 197 207 (Sept) 1944 footnote 35*e*

been recommended which supply quantities of protein far in excess of those of the 'recommended dietary allowances' of the Food and Nutrition Board[44] The cause of this increased destruction of protein is not yet understood[47]

The preceding discussion has been concerned with the quantitative aspects of the protein requirements of human beings That the dietary protein will be derived from a wide variety of foodstuffs of both animal and vegetable origin is assumed In the United States it is estimated that animal protein makes up at least 50 per cent of the protein of the usual diet If the variety of foodstuffs is limited, care must be exercised in the selection of protein The chief consideration in the choice of protein must be the furnishing of the essential amino acids to be made available to the tissues by digestion Since the optimal mixture of the essential amino acids for the nutrition of human beings is not yet known the diet must supply all the known essential amino acids in liberal amounts Animal proteins usually have a greater biologic value than do the proteins of vegetable origin Thus zein one of the proteins of the maize kernel contains no lysine or tryptophan two important essential amino acids When the diet is derived exclusively from plant materials more protein must be eaten A notable exception is gelatin This protein a product of food technology and derived from collagen completely lacks at least two essential amino acids valine and tryptophan, and contains little tyrosine and cystine, amino acids which while not essential may be important in nutrition Gelatin supplies a mixture of amino acids which is inadequate if used as the sole or chief source of these tissue building stones The recent claims for the superior food value of gelatin require further and more careful study[48] The excellent quality of the mixture of proteins present in milk is notable

Carbohydrates spare body protein The breakdown of body protein is significantly increased if the supply of the energy producing foods and particularly of carbohydrates is not ample The consideration of the total calorific value of the diet is of special importance when

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47 Lund C. C and Levenson S M Protein in Surgery J A. M A 128 95 100 (May 12) 1945 Ravdin I S Some Problems of Protein Deficiency Connecticut M J 11:7 15 (Jan.) 1947

48 The Nutritional Significance of Gelatin, report of the Council on Foods J A. M A. 107:213-2133 (Dec 26) 1936

the diet is low in its protein content, as are certain diets prescribed for therapeutic purposes Diets of high calorific content usually contain liberal or large amounts of protein

It is known that in the case of certain essential elements present in food (notably the vitamins) the nutritive value may be influenced by preservation, processing and cooking Thus the nutritive values of a natural foodstuff as determined by chemical analysis may not be a safe guide to its value when prepared for consumption Since foodstuffs which are important sources of protein are seldom consumed in the raw state, possible changes due to heat must be considered Even milk in present day practice is usually subjected to the mild heat of pasteurization The evidence in the case of proteins is conflicting The biologic value of the protein of certain legumes is believed to be increased by cooking, while the nutritive value of some other proteins (meat casein and milk products) appears to be lowered by heat [49] A detailed discussion is not possible here Whether such changes are sufficiently extensive to be of practical significance remains to be determined

No discussion of recent developments in protein metabolism can neglect the mention of the experiments of Schoenheimer in which isotopic nitrogen (N^{15}) has been used as a marker [50] These experiments indicate that a 'rapid and continuous chemical regeneration of the cell proteins is a general *characteristic of living matter* ' but despite this striking and continuous chemical activity of the organ proteins it is believed that these processes "lead to no final quantitative or qualitative changes in the composition of the tissues [51] This is in confirmation of the older belief in the constancy of composition of the structural elements of protoplasm While the observations of Schoenheimer and his group

49 Johnson L M Parsons H T and Steenbock H The Effect of Heat and Solvents on the Nutritive Value of Soy Bean Protein J Nutrition **18** 423 434 (Oct) 1939 McGinnes J and Evans R J Amino Acid Deficiencies of Raw and Over heated Soybean Meal for Chick ibid **34**: 7 5 732 (Dec) 1947

50 Schoenheimer R The Dynamic State of Body Constituents Cambridge Mass Harvard University Press, 1942

51 Schoenheimer, R and Rittenberg D The Study of Intermediary Metabolism of Animals with the Aid of Isotopes Physiol Rev **20**: 218-248 (April) 1940 Schoenheimer R and Ratner S The Metabolism of Proteins and Amino Acids in Luck J M Annual Review of Biochemistry Stanford University Calif Annual Reviews Inc 1941 vol. 10 pp 197 270

are of great physiologic significance it is not believed that at present they suggest any changes in the current practices of dietetics so far as concerns protein

In an earlier discussion (1942) of protein in nutrition I quoted Karl Thomas (1929), with reference to the chief unsolved problems of the role of proteins in nutrition No better conclusion to this presentation can be given than to reiterate the statements of Thomas[52] "What we need to know is 1 Which amino acids must be present in the food 2 How much we require of each 3 And to what purpose" Today, after more than a decade of intense interest and research in protein metabolism, these questions still epitomize the problem of the role of proteins in nutrition When they can be answered exactly the role of protein in the diet will be known and one will be able to determine the dietary value of every mixture of proteins in natural foodstuffs Until this knowledge is obtained, one may rest assured that for the healthy person, natural protein chosen from a wide variety of foodstuffs and supplied in ample amounts is the practical solution of the problem of dietary protein The body may be able to synthesize the nonessential amino acids from the essential ones, but there is no knowledge that the imposition of this task on the cells represents physiologic economy Living organisms have synthesized a wide variety of proteins containing both essential and nonessential amino acids, surely one cannot do better at present than to insure such a supply of amino acids as mixed proteins afford The gastronomic urge will prompt one to eat meat, eggs and other protein foodstuffs in preference to unappetizing protein hydrolysates or mixtures of pure amino acids

SUMMARY

Proteins are large complex molecules with colloidal properties and function as ampholytes i e, may dissociate either as acids or bases The structural units of the protein molecule are α amino acids of which some nineteen are clearly recognized as components of the usual types of proteins

Proteins are almost completely digested to the amino acids in the gastrointestinal canal, the amino acids are

52 Thomas K. Biological Values and the Behavior of Food and Tissue Protein, J Nutrition 2:419-435 (March) 1930

absorbed into the portal blood and circulate in the systemic blood from which they are rapidly removed and stored for use by the cells of the various tissues

The amino acids thus made available from the diet, may be used for the various synthetic reactions, formation of proteins and of essential products derived from amino acids (e. g thyroxine epinephrine) The amino acids not required for synthesis are deaminized with oxidation to yield ammonia and α-keto acids The ammonia is converted to urea and excreted by the kidneys

Certain amino acids, designated as essential, cannot be synthesized by the mammalian organism and must be supplied by the diet The other nonessential amino acids can be synthesized by the body

Both animal and vegetable foodstuffs are good sources of protein provided that they supply adequate amounts of the essential amino acids In the usual American dietary the amounts of protein derived from animal (meats fish milk and milk products eggs) and vegetable (cereals legumes nuts) sources are about equal

The minimal recommended protein of the diet for an adult man (70 Kg) is 70 Gm or 1 Gm per kilogram of body weight and for an adult woman 60 Gm The required amounts of dietary proteins are increased by pregnancy and lactation The requirements of the growing child are greatly in excess of those of the adult (e g 2 to 4 Gm per kilogram of body weight per day)

CHAPTER II

FAT IN NUTRITION

H C EKSTEIN

Man through his evolutionary changes has developed into an animal whose gastrointestinal tract has been modified to such a state that considerable portion of fat is desirable in his diet Although a certain amount of bulk is recognized as being of value in a complete diet, there are limits to which this should be extended When the bulk of the diet is increased by the incorporation of considerable amounts of carbohydrate, discomforts which are ascribed to abnormal fermentation in the gut are encountered McClendon,[1] in his investigation of the dietary habits of the Japanese was impressed by the prevalence of 'dyspepsia in that population and believed that the incapacitation which occurred for comparatively long periods was undoubtedly due to the high carbohydrate diet The bulk of the diet can be significantly decreased by the incorporation of additional fat, because this foodstuff supplies more than twice the number of calories available from equivalent amounts of protein or carbohydrate Unlike the other organic dietary substances fats are almost water free and this also leads to a decrease in the bulkiness Starling[1] pointed out that the human alimentary tract is so constructed that it is desirable to include from 20 to 25 per cent of the calories in the form of fat The desirability of fat in the diet was illustrated during the first great war by the experience of the German population which regarded the low daily fat allotment as one of their most serious deprivations It is common knowledge that a meal containing insufficient amounts of fat lacks in the so-called staying powers Starling[1] illustrated this by the complaints during the latter stages of the first world war of laborers that their rations were inadequate to work their normal shifts because of the low fat content Hunger was the universal reaction From a biologic

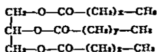
1 Cited by Anderson and Williams.[34]

point of view, it is recognized that fats are absorbed at a slower rate than carbohydrate, and, in addition, reduce the rate of discharge of gastric contents. The latter effect is ascribed to the inhibitory action of the hormone enterogastrone, the formation of which, in the intestine, is accelerated by the presence of fat.

The animal organism is well adapted to assimilate comparatively large amounts of fat. Cowgill[2] has recently reviewed the subject. Langworthy[3] studied the digestion and utilization of a considerable number of plant and animal fats by healthy adults and observed no notable variations between the behavior of the different types. The daily consumption ranged from 50 to 100 Gm. These observations and others led Cowgill to the following summation: "Edible fats the melting points of which are not too high to prevent liquefaction in the alimentary tract are digested and absorbed to about the same degree. Such differences as have been found are of no practical nutritional significance."

The influence of physical properties on the utilization of fat is well illustrated in the coefficients of digestibility of natural fats hardened to various extents by hydrogenation. Holmes and Deuel[4] observed that the degree of utilization of such products decreased significantly with the rise in melting point. The melting point of fats is to a considerable extent dependent on the chemical nature of the constituent acid radicals in the fat (triglyceride) molecule. Such fats are readily hydrolyzed in the presence of excess hydroxyl ions or specific enzymatic catalysts with the liberation of one molecule of glycerol and three of fat acids. The term "fat acids" has recently been introduced to designate the acids originating from natural fats.

In general, the acids in the fat molecule differ from one another and the term "mixed glyceride" is employed to characterize this type of lipid. This is illustrated in the following formula:



The values for x, y and z are even numbers ranging from 2 to more than 20. As a rule the chief acidic

2 Cowgill, G. W.: Relative Nutritive Values of Animal and Vegetable Fats, Physiol. Rev. 25:664 (Oct.) 1945.
3 Cited by Cowgill.

constituents of the fats in the depots and tissues of mammals contain from 16 to 18 carbon atoms It does not seem necessary to detail a listing of the numerous fat acids that have been isolated from natural sources since that information is readily available in standard texts of biochemistry It should be sufficient to call attention to the fact that fat acids fall into two distinct groups, the saturated type, most representatives of which are solid at room temperature, and the unsaturated class all members of which are liquid at this temperature Both groups belong to the same homologous aliphatic series Quantitatively, palmitic acid a saturated acid with 16 carbon atoms and oleic acid with 18 carbon atoms and 1 unsaturated double bond predominate in the depot fat of man Stearic acid the saturated acid which contains 18-carbon atoms, is occasionally present in considerable amounts in animal depot fat and when this occurs the melting point of the mixture rises When oleic acid is hydrogenated, a product identical with natural stearic acid is produced Vaccenic acid an isomer of oleic acid also gives rise to stearic acid when hydrogenated Two additional unsaturated acids linoleic and linolenic occur in abundance in certain culinary fats of plant origin. Both belong to the C-18 series, the former containing two the latter three double bonds and each in turn can be transformed into stearic acid on complete hydrogenation Fish oils contain comparatively large amounts of acid of higher molecular weight with additional double bonds

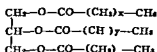
Culinary fats while they are characterized by the presence of predominating amounts of triglycerides (more than 95 per cent), also contain small amounts of the more complex lipids and usually some of the fat-soluble vitamins and pigments These complex lipids fall into three divisions the phospholipids the glycolipids (also designated as cerebrosides), and the sterols The majority of the phospholipids are closely related to the triglycerides in so far as glycerol is obtained on hydrolysis but only two fat acids are liberated The third hydroxyl group of the glycerol molecule is joined to a phosphoric acid linkage which in turn is conjugated with a nitrogenous product Three such phospholipids have been characterized lecithin in which the nitrogenous base choline is present, cephalin contain-

point of view, it is recognized that fats are absorbed at a slower rate than carbohydrate, and, in addition reduce the rate of discharge of gastric contents The latter effect is ascribed to the inhibitory action of the hormone enterogastrone the formation of which, in the intestine, is accelerated by the presence of fat

The animal organism is well adapted to assimilate comparatively large amounts of fat Cowgill[2] has recently reviewed the subject Langworthy[3] studied the digestion and utilization of a considerable number of plant and animal fats by healthy adults and observed no notable variations between the behavior of the different types The daily consumption ranged from 50 to 100 Gm These observations and others led Cowgill to the following summation 'Edible fats the melting points of which are not too high to prevent liquefaction in the alimentary tract are digested and absorbed to about the same degree Such differences as have been found are of no practical nutritional significance

The influence of physical properties on the utilization of fat is well illustrated in the coefficients of digestibility of natural fats hardened to various extents by hydrogenation Holmes and Deuel[3] observed that the degree of utilization of such products decreased significantly with the rise in melting point The melting point of fats is to a considerable extent dependent on the chemical nature of the constituent acid radicals in the fat (triglyceride) molecule Such fats are readily hydrolyzed in the presence of excess hydroxl ions or specific enzymatic catalysts with the liberation of one molecule of glycerol and three of fat acids The term 'fat acids' has recently been introduced to designate the acids originating from natural fats

In general, the acids in the fat molecule differ from one another and the term mixed glyceride is employed to characterize this type of lipid This is illustrated in the following formula



$$\begin{array}{l} CH_2-O-CO-(CH_2)_x-CH_3 \\ | \\ CH-O-CO-(CH_2)_y-CH_3 \\ | \\ CH_2-O-CO-(CH_2)_z-CH_3 \end{array}$$

The values for x y and z are even numbers ranging from 2 to more than 20 As a rule the chief acidic

2 Cowgill G W Relative Nutritive Values of Animal and Vegetable Fats Physiol Rev 25 664 (Oct) 1945
3 Cited by Cowgill[2]

the precursor of a naturally occurring antirachitic vitamin (D_3) Ergosterol, which occurs only to a small extent in animal tissues but in considerable amounts in such lower plants as yeasts and fungi, is the provitamin of vitamin D A number of additional sterols are rather widely distributed in the plant kingdom but, like ergosterol, none of these plant products are utilized to any appreciable extent by mammalia

While these complex lipids are present in only minute amounts in the culinary fats and fat depots, they do make up a major fraction of the lipids of the organs This is illustrated in the accompanying table

Consideration of the facilities for fat digestion and absorption shows that ample provision is made for the

*Distribution of Lipids in Organ and Depot Fats**

Species	Site	Phospholipids	Cerebrosides	Cholesterol	Triglycerides
Beef	Brain	5	23	19	6
Beef	Liver	70	0	4	25
Beef	Kidney	63	4	1	28
Beef	Intestine	60	3	13	24
Beef	Muscle	27	8	2	62
Beef	Butter	Trace	Trace	Trace	98+
Chicken	Egg yolk	26	2	4	66
Man	Depot	Trace	Trace	Trace	98+
Hog	Depot	Trace	Trace	Trace	98+

* All values are expressed as percentage of total lipids As will be emphasized later the content of these complex lipids particularly the phospholipids is large in the tissues of greatest physiologic importance

assimilation of considerable amounts of fat So far as the stomach is concerned splitting of fat by enzymes (lipases) is at best only of minor importance Nevertheless the organ assists materially in both digestion and absorption in that it serves as a reservoir from which the chemically unaltered fat is discharged at such a rate that the small intestine is not overtaxed The presence of fat in the meal considerably influences gastric function Fatty meals leave the stomach much slower than those with large contents of the other organic foodstuffs and when fat finds its way into the small intestine, it stimulates the production of enterogastrone, a hormone which in turn slows down gastric motility Of the enzymes having lipolytic action steapsin elaborated in the pancreas is regarded to be the chief one concerned with fat digestion Its activity is

ing aminoethyl alcohol, phosphotidyl serine in which the nitrogenous constituent is the amino acid serine of wide distribution in the proteins It is to be noted that in these lipids the ratio of nitrogen to phosphorus is 1 1 In contrast an entirely different type of phospholipid sphingomyelin, occurs in nature This contains no glycerol 1 mol of phosphoric acid, and two nitrogenous fractions, choline and sphingosine The latter an unsaturated amino alcohol of high molecular weight also occurs in the glycolipids which, in addition yield 1 mol of fat acid and one simple sugar (galactose or glucose) on hydrolysis Even more complex glycolipids the gangliosides have been described These contain 1 mol of fat acid two or three of the simple sugars and an additional nitrogenous product which has not yet been structurally characterized

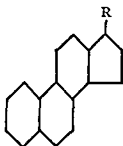


Chart showing characteristic perhydrocyclopentanophenanthrene nucleus.

The *sterols alcohols of high molecular weight belong* to a group of compounds the steroids which include the bile acids sex and adrenal cortical hormones toad poisons and the digitalis saponins All contain the characteristic perhydrocyclopentanophenanthrene nucleus shown in the chart The steroids differ from each other by variations in the composition of the side chain (*R* in the type formula), the degree of saturation of the nucleus and the number and site of attachment of hydroxyl groups on the nucleus Of the considerable number of sterols that have been isolated from natural sources *cholesterol is of paramount physiologic significance* since it is the only one which is utilized by higher animals Due to the presence of an hydroxyl group cholesterol can exist in the free or esterified form It is the chief sterol in the animal kingdom, and one of its derivatives 7 dehydrocholesterol is recognized as

fat He hypothecated the formation of an intermediate phospholipid in the resynthesis This concept gained strength from more recent work with radioactive phosphorus Data obtained with this tool[5] indicate that phospholipids are being continuously reformed in the small intestine and that, while this activity continues during inanition the rate of the reaction is considerably accelerated after the oral administration of fat

While the concept that the splitting of fat is a requisite for absorption is substantially supported by reliable and clearcut chemical findings,[6] nevertheless evidence has been presented in support of an alternate view According to Frazer of England unsplit fat passes directly into the lacteals while fat acids liberated by digestion pass directly into the portal system and at once to the liver It is beyond the scope of this article to present the data on which this view is based, and the reader is referred to Frazer's recent review[7] for such information

In considering the fate of the absorbed fat acids several pathways are open They may be incorporated into the more complex lipids deposited as such in the fat depots converted into other fat acids excreted through the gut be involved in the production of milk fat, transformed into carbohydrate or oxidized to carbon dioxide and water with the liberation of energy

As has already been mentioned the dietary acids become incorporated into the phospholipids within the intestinal mucosa Studies with hepatectomized dogs have shown that whereas the phospholipids of the small intestine can originate in these organs themselves those of the blood plasma owe their existence to the liver[8] Some years ago Bloor[6] proposed that fat acids were transported in the body in the form of phospholipids and that of these lecithin was most important The evidence for this singular role was not

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5 Fries B A Ruben S Perlman I and Chaikoff I L. The Role of the Stomach Small Intestine and Large Intestine in Phospholipid Metabolism in the Presence and Absence of Ingested Fat, J Biol. Chem. 123: 587 (April) 1938

6 Bloor W R Fat Transport in the Animal Body Physiol. Rev 2: 92 (Jan) 1922

7 Frazer A C. The Absorption of Triglyceride Fat from the Intestine Physiol. Rev 26: 103 (Jan.) 1946

8 Fishler M C. Entenman C. Montgomery, M L., and Chaikoff I L. The Formation of Phospholipid by the Hepatectomized Dog as Measured with Radioactive Phosphorus J Biol. Chem 150 47 (Sept.) 1943

accelerated by soaps and the bile acids The p_H of the small intestine (close to neutrality) also favors the catalytic action of the enzyme One of the chief properties of the bile is its ability to lower surface tension, which materially speeds up digestion of fat The small intestine secretes its own particular lipase and, under certain circumstances, this catalyst can take over the splitting of fat Data from experiments in which a partial pancreatectomy had been performed indicate that the factor of safety is large and even in the completely depancreatized dog maintained with insulin and certain lipotropic products, interference with the digestion of fat is not a problem Nevertheless the reports of the extreme diarrheas encountered in some cases of pancreatic insufficiency illustrate the importance of this organ in the utilization of fat.

It is generally accepted that the bile is the most important single secretion concerned in the absorption of fat and of the biliary constituents, the bile acids are of utmost significance Data obtained from the steatorrhea associated with obstructive jaundice clearly demonstrate that the abnormality consists not in a failure in the splitting of fat but in the impaired absorption of the fat acids liberated in digestion These bile acids are believed to combine with the water insoluble acids liberated by the lipases to form complexes which are soluble in the intestinal medium and in this form pass into the intestinal wall The pathway for the absorption of fat differs from that of protein and carbohydrate in that the major fraction of the fat enters the body through the lymphatic system Furthermore unlike the situation which prevails for the other two major organic foodstuffs the products liberated by the splitting of fat once having passed into the intestinal mucosa reunite to again form the triglyceride Phosphorylation is believed to be a factor operating in this resynthesis This conception was proposed by Sinclair[4] who observed that whereas the quantity of phospholipid in the intestinal mucosa was not increased after the ingestion of fat nevertheless the type of the individual fat acids carried by the phospholipid molecule was primarily dependent on the chemical composition of the dietary

4 Sinclair R G The Role of Phospholipids of the Intestinal Mucosa in Fat Absorption with Additional Data on the Phospholipids of the Liver and Smooth and Skeletal Muscle J Biol Chem. 82 117 (April) 1929

complete disappearance of cholesterol esters from the plasma The administration of pancreatic extracts not only remedies the situation but even results in a rise in values to somewhat above the normal level

In considering the fate of fat acids transported in this manner it should be emphasized that the current conception differs extensively from those which were popular less than two decades ago The discovery of deuterium and other isotopes and the development of methods for their preparation in suitable amounts led to biochemical investigations which practically revolutionized teachings on the fate of physiologic substances[12] Formerly it was commonly believed that dietary fats were burned soon after absorption had occurred and that when the caloric requirements of the organism had been met, any excess of fat was conveniently stored in the fat depots There it remained until the demands for energy were not fulfilled by the diet whereupon it was mobilized and burned Currently it is held that the fat depots are by no means inert materials but are tissues in a considerable state of flux Dietary fat acids merge with those of the fat depots and this mixture is constantly transported to and from the organs These newer concepts are based essentially on data secured by Schoenheimer from experiments in which fat acids labeled with deuterium were fed to white mice and rats In a typical experiment deuteropalmitic acid was fed and the fat acids of the organs and tissues fractionated Of the labeled product fed a considerable fraction (more than 40 per cent) found its way to the tissues and organs as such part was degraded to the lower homologues myristic and lauric acids another fraction was converted to stearic acid a higher homologue and an additional portion to the unsaturated acid oleic acid None of the more highly unsaturated ones linoleic and linolenic were formed In this connection mention should be made of the demonstration[13] that fat acids of this type are essential constituents in the diet of the white rat In their absence retardation of growth becomes evident renal lesions appear and untimely death occurs One of the early symptoms exhibited is scales on the feet

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12 Schoenheimer R The Dynamic State of Body Constituents, Cambridge Mass Harvard University Press 1942

13 Burr G O and Barnes R H Non Caloric Functions of Dietary Fats Physiol Rev 23 256 (July) 1943

good but more recent findings[9] indicate that the circulating phospholipids are of the choline containing (lecithin and sphingomyelin) type

Further evidence that such phospholipids play a predominating role in fat transport has been supplied by experiments with rats on diets high in fat and low in protein content Under such circumstances, fat accumulates *in large amounts (more than 30 per cent) in* the liver The incorporation of choline or of additional protein in the diet prevents this abnormal infiltration of fat This so called lipotropic effect[10] of protein is ascribed to its content of methionine, an amino acid containing a labile methyl group which can be utilized for the synthesis of choline Both methionine and choline influence lipid metabolism by accelerating the phospholipid turnover in the liver Investigations with depancreatized dogs maintained with insulin have contributed further to the problem Such animals eventually have fatty livers and, in addition exhibit a fall in the plasma phospholipids which as has been noted are primarily of the choline containing type This can be prevented by the administration of choline or extracts of the pancreas The effect of the latter cannot be accounted for entirely on the basis of the choline content and according to Dragstedt[11] this pancreatic factor, to which he has given the name 'lipocaic is a product of the internal secretion of the pancreas This has been denied by several groups of investigators particularly Chaikoff and collaborators who maintain that the factor is present in the external secretion of that gland

In addition to phospholipid it is likely that some transport of fat acids is accomplished through the medium of the cholesterol esters of the blood plasma As a rule the fat acids thus combined in the plasma are the most highly unsaturated ones in that circulating fluid and it is generally agreed that the esterification occurs in the liver In this connection it might be well to recall the striking observation that in the depancreatized dog maintained with insulin the decided rise in lipid content of the liver is often accompanied by the

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9 Taurog A Entenman C and Chaikoff I L The Choline Containing and Non Choline-Containing Phospholipids of Plasma J Biol. Chem **156** 385 (Dec) 1944

10 McHenry E W and Patterson J M Lipotropic Factors Physiol. Rev **24** 128 (Jan) 1944

11 *Dragstedt* L. R The Present Status of Lipocaic J A. M A **114** 29 (Jan 6) 1940

complete disappearance of cholesterol esters from the plasma The administration of pancreatic extracts not only remedies the situation, but even results in a rise in values to somewhat above the normal level

In considering the fate of fat acids transported in this manner it should be emphasized that the current conception differs extensively from those which were popular less than two decades ago The discovery of deuterium and other isotopes and the development of methods for their preparation in suitable amounts led to biochemical investigations which practically revolutionized teachings on the fate of physiologic substances[12] Formerly it was commonly believed that dietary fats were burned soon after absorption had occurred and that when the caloric requirements of the organism had been met any excess of fat was conveniently stored in the fat depots There it remained until the demands for energy were not fulfilled by the diet whereupon it was mobilized and burned Currently it is held that the fat depots are by no means inert materials but are tissues in a considerable state of flux Dietary fat acids merge with those of the fat depots and this mixture is constantly transported to and from the organs These newer concepts are based essentially on data secured by Schoenheimer from experiments in which fat acids labeled with deuterium were fed to white mice and rats In a typical experiment deuteropalmitic acid was fed and the fat acids of the organs and tissues fractionated Of the labeled product fed a considerable fraction (more than 40 per cent) found its way to the tissues and organs as such part was degraded to the lower homologues myristic and lauric acids another fraction was converted to stearic acid a higher homologue, and an additional portion to the unsaturated acid oleic acid None of the more highly unsaturated ones linoleic and linolenic, were formed In this connection mention should be made of the demonstration[13] that fat acids of this type are essential constituents in the diet of the white rat In their absence retardation of growth becomes evident renal lesions appear and untimely death occurs One of the early symptoms exhibited is scales on the feet

12 Schoenheimer R The Dynamic State of Body Constituents Cambridge, Mass. Harvard University Press 1942

13 Burr G O and Barnes R H Non Caloric Functions of Dietary Fats Physiol Rev 23:256 (July) 1943

Only isolated experiments have been carried out with other species In one experiment with man in which an adult was maintained for six months on an extremely low fat diet, a definite fall in the linoleic acid content of the circulating lipid was observed A similar fall has been recorded for the serum lipids of infants with eczemas Most of such cutaneous disorders were reported as cured' or "greatly alleviated' when fats containing the more highly unsaturated acids were included in the diet

The dynamic state of the tissues was demonstrated further by Schoenheimer's observation that fat acids labeled with deuterium eventually disappeared from the body even though the caloric requirements had been met In mice the half life cycle of such products ranged from five to eight days This state of flux is believed to be the physiologic explanation for the formation in the tissues of the type of fat characteristic for a particular species ingesting a diet not particularly high in fat content When, however, the diet includes considerable amounts of that foodstuff the situation is altered, and now the depot fat begins to closely resemble the dietary fat in chemical composition [14] This is of considerable economic significance to the swine husbandry industry which supplies such enormous amounts of culinary fat to the trade When for example certain vegetable foodstuffs high in a content of fat of low melting point are incorporated in the diet of hogs the so called "soft pork' grade which is more liquid than the usual type of hog depot fat is deposited While this product is unquestionably a satisfactory nutrient the market value is below that of the firmer grades Owing however to the state of flux it is *possible to remedy the situation by merely changing to* a diet containing small amounts of the liquid acids and comparatively large amounts of the saturated ones or by supplying a ration in which most of the fat has been replaced by carbohydrate In the former instance the dietary fat eventually replaces the more liquid type while in the latter case the excess of carbohydrate is transformed into the acids and these in turn are deposited

14 Anderson W E and Williams H H The Role of Fat in the Diet Phys ol Rev 17:335 (July) 1937

The physiologic transformation of carbohydrate into fat was first conclusively demonstrated by Lawes and Gilbert[15] in 1877 During the interim, repeated confirmations have been supplied, but the mechanism of the synthesis still remains somewhat obscure In recent experiments in which the body fluids of mice were enriched with deuterium the fat acids of the depots were found to contain the isotope The diet was so low in fat that a synthesis from carbohydrate must undoubtedly have taken place, and the concentration of the isotope and its distribution along the chain was such as to suggest that in this biologic process a condensation of a considerable number of small units had taken place[12] This hypothesis is further supported by the report[16] that isotopic acetic acid can be utilized for the synthesis of the higher fat acids In these experiments both the carboxyl-carbon atom and the hydrogen of the methyl group were labeled The analysis of the fat acids for deuterium resulted in data which could be best explained on the basis of the condensation of many 2 carbon units

The 2 carbon fragment is also involved in the degradation of fat acids In 1905 Knoop[17] proposed a mechanism for the oxidation of such acids whereby the long chain was oxidized at the beta carbon atom with the resulting loss of a 2 carbon unit It was further suggested that the fission progressed successively in such an orderly manner that no matter which fat acid was being catabolized eventually 1 mol of butyric acid was formed This was subsequently oxidized at the beta carbon atom with the production of the ketone bodies Knoop's contention received support from the work of Dakin[17a] who demonstrated that beta oxidation could occur in vitro and isolated some of the intermediates of the reaction The idea was further substantiated by Embden's observation[18] that the perfusion of fat acids through the liver resulted in the liberation of acetone In addition it is common knowledge that

15 Lawes J B and Gilbert J H On the Formation of Fat in the Animal Body J Anat. & Physiol. **11**: 577 1877

16 Rittenberg D and Bloch K. The Utilization of Acetic Acid for the Synthesis of Fatty Acids J Biol. Chem. **160** 417 (Oct.) 1945

17 Knoop F Der Abbau aromatischer Fettsauren im Tierkörper Beitr z chem Phys u Path. **6** 150 1904

17a Dakin H D Oxidations and Reductions in the Animal Body London Longmans Green & Co. 1912

18. Embden G., and Wirth J Beitrag zur Lehre vom Abbau der Fettsauren im Tierkörper Verhandl. d. Kong f inn. Med. 1909 p 347

ketone bodies are formed during the catabolism of fat by man In the healthy person the urinary excretion of such ketones is increased by the excessive oxidation of fat as it occurs on a high fat diet or as in fasting *For the same reason ketonemia and ketonuria are com* mon occurrences in uncontrolled diabetes mellitus While this classical theory whereby oxidation occurs at the beta carbon atom has stood the test of time the corollary that the oxidation of 1 mol of any particular fat acid gives rise to only 1 mol of the ketone body, is currently not accepted Stadie[19] has recently reviewed the literature on this phase of the problem Two alternate proposals have been made One of these first suggested by Hurtley[20] in 1916 and revived by Jowett and Quastel [21] in 1935 postulates that the chain is oxidized simultaneously along its whole length at alternate carbon atoms beginning at the beta position As a result the whole molecule is converted into ketones which break up to form 4 carbon chains Accordingly, beta oxybutyric acid is again formed but under these circumstances butyric acid would yield 1 mol, octanoic 2 lauric 3 and palmitic 4 mols of the ketone bodies Previously it was assumed that only 1 mol would arise from all of the acids While this newer suggestion is compatible with a considerable amount of data accumulated from experiments with liver slices as well as with healthy intact animals divergent reports are also available Thus the 5 carbon chain of valeric acid gives rise not only to glucose but also to acetone suggesting the condensation of two 3 carbon chains to form the sugar and of two 2 carbon fragments to give rise to the ketone Other acids containing an odd number of carbon atoms have been shown to be both glucogenic and ketogenic In addition Deuel and co-workers observed a greater increase in the ketone excretion following the oral administration of hexanoic acid to the intact white rat than when butyric acid was given These and other observations led MacKay to propose that oxidation of fat acids proceeded at the beta carbon

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19 Stadie W C. The Intermediary Metabolism of Fatty Acids Physiol Rev **25** 395 (July) 1945

20 Hurtley W H The Four Carbon Atom Acids of Diabetic Urin Quart. J Med **9**: 301 1916

21 Jowett M and Quastel J H Studies in Fat Metabolism Biochem. J **29** 2143 2159 and 2181 (Sept.) 1935

22 MacKay E M *Significance of Ketosis* Review Article, J Clin. Endocrinol. **3** 101 (Feb) 1943

atom, as suggested by Knoop, but that the 2 carbon fragment, liberated in this manner, recombined to form the ketone bodies The report that acetic acid, administered per os to rats, is converted to aceto-acetic acid is in good accord with this conception Furthermore when octanoic acid, containing the C^{13} isotope in the carboxyl group was equilibrated with liver slices the distribution of the tag in the isolated aceto acetic acid was in close agreement with values predicted on the basis of this beta oxidation condensation theory Schoenheimer's[12] observation that deuteropalmitic acid gives rise to deuteromyristic acid is further proof for the removal of the 2 carbon fragment On the other hand Stadie[19] pointed out that some experiments with beta hydroxybutyric acid led to data more in accordance with values to be expected on the basis of multiple alternate oxidation as proposed by Hurtley[0] Evidently both mechanisms can operate, and at present it seems advisable to defer judgment concerning the predominance of either path

According to Verkade[23] still another path is open for the catabolism of fat acids In this scheme the terminal methyl group is first oxidized with the formation of a dicarboxylic acid which is in turn successively oxidized at the two positions beta to the carboxyl groups While there is some experimental justification for this proposal it is generally believed that, even though this so called omega oxidation may operate the amounts of acids thus catabolized are so minimal that in the end this route is of little physiologic importance

It is generally agreed that the complete oxidation of fat acids to carbon dioxide and water takes place in two stages The initial one, which occurs almost exclusively in the liver, results in the formation of the ketone bodies already referred to It has been reported[4] that the presence of adenosine triphosphate, or a system giving rise to it is necessary for this first phase The second one which takes place almost entirely in the extrahepatic tissues, particularly the kidneys and muscles consists of the disposal of the 4 carbon chain with the production of water and carbon dioxide It

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3 Verkade P E The Role of Dicarboxylic Acids in Metabolism Chem. & Ind. 57:704 1938

4 Lehninger A L. The Relationship of the Adenosine Polyphosphates to Fatty Acid Oxidation in Homogenized Liver Preparations, J Biol. Chem 157:363 (Jan.) 1945

has been suggested that certain intermediates which also have been found to operate in the final disposal of carbohydrate are involved in the ultimate breakdown of fat Direct evidence for this idea has been supplied by Buchanan and others,[25] who incubated tagged acetate and aceto acetate with kidney homogenates and detected the isotope (C^{13}) in the alpha keto glutaric, fumaric and succinic acids isolated from the reactions mixture All three had previously been shown to be members of the tricarboxylic acid cycle involved in carbohydrate catabolism

While it is probable that the 2 and 4 carbon metabolites can be disposed in the manner described, sight should not be lost of other paths for the utilization of the acetate fragment Thus the conversion of this short chain to the higher fat acids has been demonstrated the synthesis of cholesterol from acetate accepted and the utilization of the acetyl group for the detoxication of certain amines established Acetate and aceto acetate have also been assigned the role of intermediates by some investigators in their proposed scheme for the conversion of fat to carbohydrate This issue continues to be exceedingly controversial and while some of the more recent findings favor the interconversion an evaluation of the evidence available generally leads to the verdict that the case has not been proved

Fat acids need not follow any of the pathways outlined This is illustrated in studies on the origin of milk fat Currently it is held that the major portion of such fat arises directly from the triglyceride fraction of the blood lipids and that the chemical composition of it is in turn governed to a considerable extent by the dietary habits of the host Hilditch [26] of England has clearly established that the chemical nature of the milk fat of the dairy cow can be significantly altered by dietary management However this comparatively simple explanation does not account for all the facts observed in this phenomenon Butter obtained from the dairy cow for example contains unusually large amounts (8 to 10 per cent) of fat acids containing 4 to 10 carbon atoms Similarly observations are recorded

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25 Buchanan J M Sakami W Gurin S and Wilson D W A Study of the Intermediates of Acetate and Aceto-Acetate Oxidation with Isotopic Carbon J Biol Chem **159** 695 (Aug) 1945

26 Hilditch T P The Chemical Composition of Natural Fats New York John Wiley & Sons Inc 1940

for the milk fat of other ruminants but the distribution of the individual constituents within this fraction varies significantly with the species In contrast the milk of the pig the dog and the human being contains almost negligible amounts of these acids of low molecular weight resembling in this respect almost all other natural fats These inconsistencies cannot be ascribed to differences in dietary habits Man is notable for his continued ingestion of cow's milk even after maturity has been attained This does not occur in the dairy cow If these particular acids are dietary in origin the milk fat of the lactating woman should of necessity contain more and not less of such acids of low molecular weight It has been suggested that the source of these fatty acids in the milk of ruminants may be from the fermentation which takes place in the stomach In this connection it should be recalled that such acids are not deposited in significant amounts in the tissues of the rat even though they may be supplied in abundant amounts in the diet These observations and others have led to a belief that fat acids of low molecular weight are actually synthesized in the mammary gland and that the variations in the distribution of them in the milks of different species are to be ascribed to metabolic differences in their respective glands

Cowgill[2] in his review devoted considerable space to the controversy on the relative nutritive value of butter fat and the margarines He referred to the work by Schantz Elvehjem and Hart of Wisconsin who compared the nutritive value of mineralized milk rations supplemented separately with a variety of vegetable fats and butter, and concluded that during their early life young rats receiving the ration containing the butter fat showed the best response in growth In additional experiments these workers obtained data which led them to believe that butter fat is superior to the margarines so far as growth of young rats is concerned The same group[27] recently determined the vaccenic acid (an isomer of oleic acid) content of a variety of fats and oils and reported that whereas the acid is present in small amounts (less than 0 85 per cent) in butter fat, lard and beef fat none was detected

[27] Geye R P Nath H, Bark V H, Elv hjem C. A. and Hart E. B The Vaccenic Acid Content of Various Fats and Oils J Biol. Chem 169:427 (June) 1947

in the number of vegetable fats examined This study followed a report [8] that the growth of rats on a ration containing rape seed oil as the source of fat was inferior to the rate observed when butter alone was employed as the dietary fat The inclusion of 0 1 per cent of vaccenic acid in the rape seed oil diet resulted in a growth rate which practically duplicated the one recorded for the ration containing butter It was suggested that superiority of butter fat over the margarines was due to the presence of vaccenic acid

According to Cowgill Deuel and collaborators were unable to demonstrate this superiority of butter In a comprehensive investigation of the problem this latter group observed satisfactory growth and reproduction of ten generations of rats during which time the butter fat of a ration known to be satisfactory for growth and reproduction was replaced by a margarine Other investigators agreed with Deuel In this connection the latter has remarked on the observation by Hilditch that human milk fat more closely resembles the margarines in chemical composition than does the fat obtained from the milk of the dairy cow It should be pointed out that experiments have not been conducted with human subjects and that differences observed in the rat may not apply to man In commenting on this problem Cowgill pointed to the differences in the rations employed the strains fed and the conditions under which the investigations were carried out by the several groups and suggested that the matter might be clarified by providing uniform conditions in future studies

Turning now to the problem of the utilization of the complex lipids it is evident that our knowledge of the digestion and absorption of these is scanty With regard to the phospholipids most of the data are limited to the lecithins These are believed to be split by enzymes in the duodenum At least this is the conclusion reached from data obtained on the composition of the thoracic lymph collected before and after the feeding of these particular phospholipids To date it has not been established whether lecithins can enter the portal blood stream directly in the unsplit form Studies

28 Boer J Jansen B C P and Kent e A On the Growth Promoting Factors for Rats Present in Summer Butter J Nutrition 33 339 (March) 1947

on the utilization of cephalin and phosphotidyl serine have not been recorded, and those pertaining to sphingomyelin are fragmentary. With regard to the cerebrosides the data available in the literature are few and conflicting. It is clear that this phase of lipid metabolism needs investigation. From some unpublished work obtained in this laboratory it is apparent that the lipid fraction of the brain which contains considerable portions of all of these complex lipids, is reasonably well utilized, but not as well as the triglycerides. These studies have however not been carried beyond the preliminary stages.

In contrast to the lack of information referred to, the literature contains numerous investigations on the utilization of cholesterol and its esters. Much credit should be given to Gardner, of England who initiated so many significant studies on the origin and fate of this sterol. As a consequence of the analysis of thoracic lymph, following the feeding of cholesterol and its esters it has been established that regardless of whether fed in the free or esterified form, increases in both fractions occur in the lymph. This indicates that during absorption both esterification and hydrolysis occur in the small intestine. As a rule the absorption of cholesterol takes place best in the presence of dietary fat. This may be due to supplying fat acids for esterification. As in the case for fat the absorption of cholesterol is accelerated by the presence of bile and it is believed that this is accomplished by a combination of the alcohol with bile salts with the formation of soluble complexes.

It is agreed that all these complex lipids can be synthesized by higher animals from comparatively simple products. This is illustrated by experiments with rats on diets practically devoid of such lipids. In such circumstances growth occurred with a corresponding rise in the content of these lipids in the tissues. Similarly it is evident that such lipids increase in amount in the suckling infant even though the milk contains insufficient amounts to account for the increment. According to Block and Rittenberg[9] acetic acid when fed to mice and rats leads to the synthesis of cholesterol. The deuterium in the dietary acetate was present in both the nucleus and the side chain of the steroid.

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[9] Block K and Rittenberg D On the Utilization of Acetic Acid for Cholesterol Formation, J Biol. Chem. 145: 6_5 (Oct.) 1942

Mention has already been made of the role of the phospholipids in fat absorption and transport In addition they undoubtedly are intimately associated with other physiologic activity, inasmuch as the more active tissues contain the larger amounts of such lipids Heart muscle for example contains practically twice as much as skeletal muscle These lipids are intimately associated with protein and it is believed that the lipids of *blood plasma are combined with protein* The prosthetic group in the thromboplastic protein of plasma and tissues so intimately associated with the clotting of blood is considered to be a complex lipid of the phospholipid type The role of cholesterol in the living organism is undoubtedly a manifold one Its presence in practically all tissues indicates this However, it is not possible to describe all of its various functions Mention has already been made of its relationship to the natural form of vitamin D In addition it can give rise to the bile acids and some of the sex hormones Analyses of normal tissues have proved the presence of a variety of degradation products of cholesterol which conceivably can be considered to be the precursors of additional hormones

The distribution of these complex lipids in the blood during the postabsorptive state and in the organs does not vary materially over considerable lengths of time in the healthy subject As a rule the lipids levels in the corpuscles remain unaltered during disease but definite fluctuations from the normal values are encountered in the plasma The fall in cholesterol esters observed in diseases of the liver is ascribed to a failure in formation in that organ Falls in total cholesterol values have been observed in certain infections while hypercholesterolemia often accompanies nephrosis The levels of plasma cholesterol vary appreciably with thyroid activity *being subnormal in hyperthyroidism* and elevated above normal in hypothyroidism The reader is referred to Bloor s monograph [30] for references to and a more detailed discussion of the variations in the levels of the plasma lipids under pathologic conditions *The role of the lipids in atherosclerosis* has recently been reviewed [31]

30 Bloor W R Biochemistry of the Fatty Acids and Their Compounds the Lipids New York Reinhold Publishing Corporation 1943

31 Hirsh E F and Weinhouse S The Role of Lipids in Atherosclerosis, Physiol Rev 23: 185 (July) 1943

Variations from the normal lipid content are encountered in the organs of a number of pathologic conditions grouped as the 'lipidoses' One of these the xanthomatoses is characterized by a deposition of cholesterol in large quantities in the tissues In the xanthomatosis of the bones and organs and in the Schüller-Christian syndrome the plasma cholesterol levels are not elevated whereas a definite hypercholesterolemia is commonly observed in xanthoma tuberosum In the latter condition the treatment of the disease by prescribing a cholesterol-low or plant diet has been reported as successful On the other hand some patients do not respond in this manner to the change in diet In Niemann-Pick disease the disorder is in the accumulation of sphingomyelin while in infantile amaurotic familial idiocy (Tay-Sachs disease) the gangliosides increase extensively Gaucher's disease is characterized by the deposition of large amounts of the cerebrosides, particularly in the spleen In contrast to galactose, as is the case for the cerebrosides of the healthy subject, glucose was found to be the carbohydrate constituent of the lipid With the exception of some of the xanthomatoses the levels of the individual lipids in the plasma in these pathologic conditions fall within the normal range, and no satisfactory explanation has been made for these unusual situations A detailed description of these anomalies and speculations concerning their origin are available in a recent review [32]

SUMMARY

1 The incorporation of suitable amounts of fat (triglycerides) in the diet increases the 'staying power' of the ration and the substitution of fat for carbohydrate decreases fermentation in the gut

2 Triglycerides of plant and animal fats are equally well digested and absorbed provided that liquefaction of these occurs in the small intestine Plant sterols are not absorbed to any significant extent by man while cholesterol the chief sterol of higher animals is well utilized.

3 Depot fats consist primarily of triglycerides In contrast, cholesterol the phospholipids and the cerebrosides occur in predominating amounts in the actively functioning organs of animals

32 Thannhauser S J and Schmidt G Lipids and Lipidoses, Physiol. Rev 26 : 275 (April) 1946.

Mention has already been made of the role of the phospholipids in fat absorption and transport. In addition they undoubtedly are intimately associated with other physiologic activity inasmuch as the more active tissues contain the larger amounts of such lipids Heart muscle for example contains practically twice as much as skeletal muscle These lipids are intimately associated with protein and it is believed that the lipids of blood plasma are combined with protein The prosthetic group in the thromboplastic protein of plasma and tissues so intimately associated with the clotting of blood is considered to be a complex lipid of the phospholipid type The role of cholesterol in the living organism is undoubtedly a manifold one. Its presence in practically all tissues indicates this However it is not possible to describe all of its various functions Mention has already been made of its relationship to the natural form of vitamin D In addition it can give rise to the bile acids and some of the sex hormones Analyses of normal tissues have proved the presence of a variety of degradation products of cholesterol which conceivably can be considered to be the precursors of additional hormones

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31 Hirsh, E. F and Weinhouse S The Role of Lipids in Atherosclerosis, Physiol. Rev 23 185 (July) 1943

CHAPTER III

CARBOHYDRATE METABOLISM

DeWITT STETTEN JR.

ENERGY CONSIDERATIONS

Many of the individual processes which when taken together comprise the normal body economy when considered as isolated systems prove to be endergonic that is energy-consuming processes incapable of continued operation unless the needed energy is supplied in one or another fashion By way of preface to a discussion of the role of carbohydrates in the total mammalian metabolism it may be well to tabulate some of these endergonic processes in order that insight may be gained into the disposition of the relatively enormous amounts of energy that the normal organism derives from the breakdown of carbohydrates each day (*a*) the maintenance of body temperature at a level in general above that of the environment (*b*) the performance of mechanical work both voluntary and involuntary incident to muscle contraction (*c*) the initiation and transmission of neural impulses (*d*) the secretion or reabsorption of tissue and blood constituents often against a concentration gradient and (*e*) the continuous regeneration of the large molecules of protein polysaccharide and fat which make up the major portion of the organic components of protoplasm for the synthesis of which not only the small building stones but also a supply of energy is needed

These and other processes are continuously consuming energy and this energy deficit must ultimately be met by the caloric supply of the diet if the organism is to remain in balance The incidental energy requirements of growth pregnancy lactation tissue repair and wound healing must also be derived from this source and in view of the fact that in a perfectly normal dietary well over half of the calories of the diet may appear in the form of carbohydrate it is of obvious

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4 Pancreatic lipase and the bile salts are the chief factors in the digestion and absorption of triglycerides from the intestine

5 Choline containing phospholipids are intimately associated with the transport of fat acids in the body These acids may be incorporated in the complex lipids, deposited in the fat depots converted to other fat acids excreted into the gut utilized in the formation of milk fat or oxidized to carbon dioxide and water with the liberation of energy

6 While the majority of the fat acids can be synthesized by the animal organism linoleic and linolenic are apparently exogenous in origin Either one of the latter two is an essential constituent in the diet of the white rat and may be required by man

7 Degradation of fat acids takes place in two stages The first phase occurring almost exclusively in the liver consists in the production of the ketone bodies which are disposed of in the final stage in the extra hepatic tissue (notably in the kidneys and muscles)

8 With the exception of those of low molecular weight (C_4 to C_{10} inclusive) the fat acids of milk fat originate from the triglycerides of the blood The composition of milk fat can be altered by dietary management The controversy on the comparative nutritive value of butter and the margarines still exists

9 Cholesterol the phospholipids and the cerebrosides can be synthesized by the animal organism Increased deposition of these occurs in the actively functioning organs in the different types of lipidoses

small and intimately associated with this fact the hydrolysis as written is readily reversible and the possibility exists that the compound may arise and accumulate to an appreciable extent as a result of spontaneous synthesis from its parts Such compounds are said to contain 'low energy phosphate.' There are on the other hand numerous compounds of phosphoric acid which, when subjected to hydrolysis yield large amounts

Types of Compounds of Phosphoric Acid

Type	Structure	Energy of Hydrolysis	Examples
Phosphoric ester of simple alcohol	H R —C—C—O—P(=O)(OH)—OH H	Low	Glucose-6-phosphate 3-phosphoglyceraldehyde 2 phosphoglyceric acid
Phosphoric acid acetal	—O —C—C—O—P(=O)(OH)—OH H	Low	Glucose 1 phosphate 1,3 diphosphoglyceraldehyde (the 1 phosphate)
Anhydride of phosphoric acid	O —O—P(OH)—O—P(=O)(OH)—OH	High	Adenosine triphosphate adenosine diphosphate
Mixed anhydride of phosphoric acid	O —C—C—O—P(=O)(OH)—OH	High	Acetyl phosphate 1,3-diphosphoglyceric acid (the 1 phosphate)
Enol phosphate	—C=C—O—P(=O)(OH)—OH C	High	Phosphopyruvic acid
N substituted phosphamic acid	—C—N—P(=O)(OH)—OH H	High	Phosphocreatine phosphoarginine

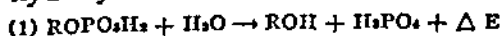
of energy in regard to the foregoing equation, ΔE is a large quantity The hydrolysis of such compounds proceeds essentially irreversibly and completely and such compounds cannot be pictured as arising to any appreciable extent from spontaneous interaction of the products of hydrolysis These compounds are referred to as high energy phosphate compounds

Included in the table are examples of these two types of compounds of phosphoric acid In relation to this table, it should be pointed out that it is thermodynam-

importance to understand what little is known of the means whereby the energy, made available to the organism by the breakdown of carbohydrate, is delivered to these various energy consuming processes

The primitive idea that sugar is burned in the animal body as it might be burned in a furnace and that the heat liberated thereby is the source of energy for muscle work has long been recognized as untenable The efficiency of the transfer of usable energy through the mode of heat is limited by the fraction $\frac{\text{temperature difference}}{\text{absolute temperature}}$ and such processes become efficient only when a large temperature difference can be achieved Thus at body temperature assuming a thermal difference of 10° C to occur no more than one thirtieth of the energy liberated by the combustion of sugar would be available for the performance of useful work Yet isolated muscle has been shown to operate on a nutrient of glucose with vastly greater efficiency than 3 per cent despite the fact that no significant thermal differences within the muscle have been shown to occur From this it follows that a large portion of the energy liberated by the breakdown of glucose in the mammalian cell must be delivered to systems capable of accepting energy and transforming it into useful work without the intervention of the energy-mode of heat Recognition of this fact gave rise to the concept of 'energy-linked processes' wherein the energy released by one reaction is immediately accepted and utilized by some other reaction occurring simultaneously After a generation of exploration one may now point to one such energy link which has clearly been proved to be operative in biologic systems and which must serve as an example of the devices which have evolved to accomplish the necessary energy transfer

The biologically important compounds of phosphoric acid [1] have been shown to fall roughly into two groups and this division is based on the amount of energy which is released when these compounds are subjected to hydrolysis If one considers the reaction type



(1) $ROPO_3H_2 + H_2O \rightarrow ROH + H_3PO_4 + \Delta E$

where Δ E is the energy released one sees that of some compounds of phosphoric acid the quantity Δ E is

1 Lipmann F in Nord F F and Werkman C H Advances in Enzymology New York Interscience Publishers Inc. 1941 vol 1 p 99

energy phosphate compound in the vicinity, and contraction accompanied by the performance of mechanical work on the environment, release of kinetic energy decrease in potential energy and loss of phosphate as inorganic phosphate ions at an energy level of 0 Such a process may be repeated continuously as long as there is a supply of compounds of phosphoric acid of the energy rich variety available in the neighborhood, in muscle tissue such a reservoir is at hand (fig 1) The terminal phosphoric acid residue of adenosine triphosphate appears to be the immediate source of high energy phosphate for the recharging of the contracted myofibril Backing up this reservoir there is a second reservoir

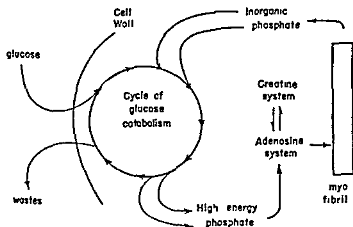
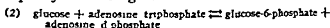


Fig 1—The role of high energy phosphate in the transfer of energy from glucose catabolism to effector organ (Adapted from Lipmann F in Nord F F and Werkman C. H Advances in Enzymology vol. 1 p 12 [1941])

in the form of the creatine phosphate which is abundant in striated muscle By virtue of these reservoirs an isolated muscle may be made to undergo repeated con tractions even though carbohydrate catabolism may have been completely inhibited by the use of suitable poisons Inevitably however in such a preparation these reservoirs of high energy phosphate will soon be depleted the high energy phosphate necessary to recharge the myofibrils will no longer be available and muscle work will come to a standstill

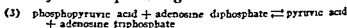
It is at this point that the role of glucose catabolism in the working cell must be taken into account One

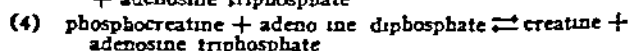
ically possible for any compound of high energy to surrender its phosphate residue to some acceptor and generate a phospho-compound of low energy, whereas the reverse cannot occur An example of a reaction of this type is the well known hexokinase-catalyzed phosphorylation of glucose


(2) glucose + adenosine triphosphate ⇄ glucose-6-phosphate + adenosine d phosphate

Here a low-energy phosphate bond has been established at the expense of a high-energy bond

Of the several high energy compounds listed in the table by way of generalization it may be stated that the energies of hydrolysis of all of these compounds are of the same order of magnitude This fact gives rise to the thermodynamic possibility of the generation of a new high energy phosphate bond at the expense of another high energy bond, and furthermore since the net gain or loss of energy in such a reaction will be small such a reaction may be expected to proceed reversibly Examples are given herewith


(3) phosphopyruvic acid + adenosine diphosphate ⇄ pyruvic acid + adenosine triphosphate


(4) phosphocreatine + adeno ine diphosphate ⇄ creatine + adenosine triphosphate

The energy link believed to intervene between the catabolism of glucose on the one hand and the contraction of muscle on the other is closely related to such shuttling about of high energy phosphate The current picture describes the contractile unit of the myofibril as existing in two states an extended and a contracted state. In the extended or elongated condition it is rich in potential energy like an extended spring As it contracts with the generation of kinetic energy it loses potential energy precisely as is the case with a stretched spring that is permitted to contract and before it can do any more work it must be recharged with energy and reconverted to the extended condition This transformation is apparently accompanied by and closely related to the introduction into the myosin unit of phosphate and what is of importance to the present discussion the phosphate required is of the high energy variety The continuous operation of a muscle fiber may be pictured as being made up of two alternating phases extension accompanied by an increase in potential energy and the coincident introduction of high energy phosphate at the expense of some high

mammal is obviously incapable of synthesizing its full supplement of glucose from carbon dioxide and water a synthesis that is effectively carried out by certain micro-organisms and chlorophyll-containing plants There are three sources of blood glucose that come into consideration and of these the most important one quantitatively is the carbohydrate of the diet The other contributions to the blood glucose may be classified under the headings of glycogenolysis and gluconeogenesis

The carbohydrates of the diet that are of nutritional significance are surprisingly few in number (fig 2)

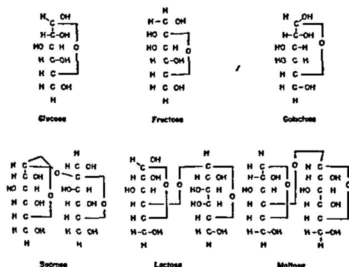


Fig 2—Formulas of the nutritionally important sugars

Only three monosaccharides glucose fructose and galactose need be mentioned and although the first two of these do occur as such in various fruits, it is questionable whether any of these three ever comprises a major portion of a normal diet Of the disaccharides sucrose the common sugar of cane and beet is of course a variable dietary component and lactose the carbohydrate of milk is obviously of significance in infant nutrition Maltose is of interest not so much as a naturally occurring product but rather as an intermediate in the breakdown of larger polysaccharide

of the important consequences of the breakdown of glucose in the living cell is the generation of new high energy phosphate compounds in the formation of which glucose is catabolized and inorganic phosphate ions are consumed Examples of individual reactions in which such high energy phosphate compounds arise will be given later in the text Suffice it to state at this point that, per molecule of glucose degraded to pyruvate or lactate, two high energy phosphate bonds, according to current understanding, will have been created *de novo* As the high energy phosphate which arises incident to the breakdown of glucose is transferable to adenosine diphosphate, to regenerate adenosine triphosphate and secondarily creatine phosphate, the processes of normal glucose catabolism tend to offset the depletion of high energy phosphate stores that would otherwise result from continued muscle work

This energy link between the breakdown of glucose and the performance of muscle work, involving the repeated generation and destruction of high energy phosphate must not be supposed to be peculiar to this system Indeed, at least one other endergonic process, the generation of polysaccharides has been shown to be linked energetically to glucose breakdown through the same type of shuttling about of phosphate residues (discussed later), and it may be supposed that other energy-consuming processes operate in the cell which is destroying glucose by virtue of this same energy link It must however be borne in mind that energy links in addition to the one described may yet be unearthed and, indeed at the present time one is able by reactions known to occur to account for the disposition of only a small fraction of the energy liberated in the complete oxidation of glucose to carbon dioxide and water

SOURCES OF GLUCOSE

The glucose on which the cells of the mammalian organism depend to a greater or lesser extent for their continued nutrition is of course the glucose dissolved in the extracellular fluids of the body of which the blood plasma may be taken as representative Whereas it is undoubtedly true that some mammalian cells retain a vestigial capacity to assimilate carbon dioxide[2] the

2 Buchanan J M and Hastings A B Physiol Rev 26: 120 1946

stomach ptyalin is rapidly inactivated by the acidic environment which it encounters so that enzymic digestion comes to a standstill. A small degree of digestion in the stomach incident to the catalysis of hydrogen ions has been postulated.

The small intestine is the major site both of polysaccharide digestion and of absorption of the resultant simple sugars. Pancreatic amylase and the glucosidases of the succus entericus both participate in catalyzing the hydrolysis of glucosidic links and the ultimate disintegration of the complex sugars of the diet to the monosaccharide level.

Derived from the carbohydrates of the diet one may expect to see in the lumen of the small intestine a mixture of glucose, fructose and galactose, and, except for that portion which undergoes bacterial fermentation these monosaccharides are delivered to the portal blood stream in a quantitative fashion. The transport of these hexose molecules across the intestinal mucosa appears not to be simply a matter of diffusion since the rate of this transport is in general independent of the concentration gradient against which it is operating. It appears to be a vital process dependent in some fashion on the reaction of phosphorylation and probably is not dissimilar to the process of reabsorption of glucose from the renal tubule. The several sugars are absorbed from the intestinal canal at widely differing rates the order of these rates being galactose > glucose > fructose > mannose > pentoses.[3]

Glucose is certainly the most abundant hexose entering the bloodstream from the intestinal tract. Galactose and fructose, insofar as they are absorbed and enter the processes of glycolysis and glycogenesis may be presumed to be capable of ready transformation into the glucose configuration. Of the various monosaccharides of metabolic interest, galactose is formed abundantly and excreted as lactose in the process of lactation and also crops up as the characteristic sugar in many cerebrosides; ribose and desoxyribose are formed from unknown precursors in the body and appear in the nucleic acids and nucleotides and xyloketose appears as a urinary constituent in pentosuria. From the nutritional point of view however, the concern is predominantly with glucose.

[3] Cori, C. F. J. Biol. Chem. 66: 691 1925

molecules The hydrolysis of each of these disaccharides gives rise to a pair of monosaccharide molecules

(5) sucrose → glucose + fructose
(6) lactose → glucose + galactose
(7) maltose → glucose + glucose

The major portion of the usual dietary carbohydrate is made up of polysaccharides, compounds of large and imperfectly known molecular size The starches of vegetable origin, and glycogen of animal origin are the important members of this group, and both are made up of glucose fragments linked to each other in what is termed 'glucosidic linkage, in which the number 1 carbon of one glucose unit is coupled through an oxygen bridge to the number 4 or number 6 carbon of an adjacent glucose unit On complete hydrolysis of these materials the sole carbohydrate obtained is glucose

The remaining carbohydrates of the diet are of little nutritional importance The pentoses, such as xylose and arabinose which may be present in the diet to a scant extent are known to be absorbed across the intestinal mucosa much more slowly than the common hexoses and little is known of their further metabolic utilization Polysaccharides which on hydrolysis yield pentoses are represented among the gums such as gum arabic and acacia as well as agar, but these are not digested or absorbed and serve merely to increase the bulk of the intestinal contents Similarly cellulose, a polysaccharide of glucose although apparently digested by certain ruminants is not subject to digestion by the gastrointestinal enzymes and serves only as roughage.

The digestion of carbohydrates like the digestion of proteins and fats may be described as a series of enzyme-catalyzed hydrolyses in which the large molecules of the diet are broken down to smaller unit fragments preparatory to their absorption It is generally believed that the bulk of dietary carbohydrate is degraded to the monosaccharide level prior to absorption although small amounts of disaccharide such as sucrose may be absorbed without hydrolysis The first of the enzymes, in the most general sense glucosidases to operate on ingested polysaccharide is the salivary amylase ptyalin In view of the short duration of contact between dietary polysaccharide and active ptyalin the extent of digestion accomplished by this enzyme is probably small When the bolus of food enters the

stomach ptyalin is rapidly inactivated by the acidic environment which it encounters so that enzymic digestion comes to a standstill. A small degree of digestion in the stomach incident to the catalysis of hydrogen ions has been postulated.

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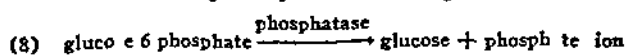
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[3] Cori C F J Biol Chem. 66 691 1925

In addition to the absorption of the products of carbohydrate digestion from the intestinal canal there are two other types of processes which contribute to the blood glucose and these are conveniently discussed under the headings of gluconeogenesis and glycogenolysis Under the term gluconeogenesis may be included all reactions which originate with noncarbohydrate precursors and terminate with the generation of glucose Among the materials which the body is capable of employing in this fashion are (*a*) essentially all of the products that the body can generate from glucose down to and including the four-carbon dicarboxylic acids (*b*) all of the amino acids that are capable of being transformed into or of contributing carbon atoms to any of the foregoing intermediates—such amino acids comprise the glucogenic amino acids—and (*c*) certainly glycerol and, according to some authorities possibly the fatty acids which may arise from the hydrolysis of fat

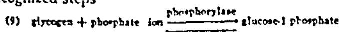
Since in general the reactions of glycolysis glucose breakdown may proceed in both directions in the body, the products of glycolysis would be expected to be glucogenic Certain of these products however may arise from other sources Thus, α ketoglutaric acid may be formed from glutamic acid and presumably from the other five carbon amino acids as well and oxaloacetic acid can certainly arise from the amino acid aspartic acid The three carbon amino acids alanine, serine and cysteine may contribute their carbon skeletons to form pyruvic acid and glycerol is similarly interconvertible in the body with certain of the three carbon fragments that arise from the breakdown of glucose When proceeding in the direction of glucose formation these processes all funnel into the formation of glucose 6 phosphate This compound in common with other phosphorylated compounds appears to cross cell membranes slowly, if at all and is believed to be utilized for the most part in the very cells in which it is formed The enzyme required for the catalysis of the irreversible hydrolysis of this product

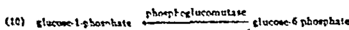

(8) gluco e 6 phosphate $\xrightarrow{\text{phosphatase}}$ glucose + phosph te ion

appears not to be uniformly distributed and while it is abundantly present in liver it is lacking in striated muscle Thus, whereas the liver is well able to con-

tribute to the blood glucose as a result of gluconeogenic processes such processes in muscle result in the augmentation of some other product, notably glycogen

The third source of blood glucose to be considered is the breakdown of glycogen This proceeds over well recognized steps [4]


(9) glycogen + phosphate ion ⇌(phosphorylase) glucose-1 phosphate


(10) glucose-1-phosphate ⇌(phosphoglucomutase) glucose-6 phosphate

The glucose-6-phosphate which arises as a result of these reactions is of course subject to the same restrictions described in that in liver but not in muscle it may be hydrolyzed to yield glucose (reaction 8) A consequence of this enzymic deficiency of striated muscle is the fact that muscle glycogen cannot contribute directly to the blood glucose, that the first products of glycogen breakdown in muscle that can escape readily from the muscle cell are pyruvic and lactic acids and that only as these do escape and are captured by the liver and employed there for gluconeogenesis can muscle glycogen contribute to the glucose of the blood

GLYCOLYSIS

In summing up the sources of blood glucose it may be pointed out that in a quantitative sense the breakdown of glycogen constitutes a much smaller contribution than do the other two processes and appears to be of major importance only in times of acute stress It should also be stressed that all three processes are undoubtedly operating continuously in the normal subject and this leads to a consideration of the fate in the animal body of the glucose thus made available. In the normal subject, essentially all of this glucose is consumed in one way or another no appreciable amounts appearing in the excreta Many metabolic pathways and many hypothetic intermediates have at one time or another come into consideration The pathways and the intermediates presented herewith are those currently acceptable and well established experimentally but should not be construed as the only possible routes over which glucose can be utilized Rather should this scheme be considered as a highly probable series of

[4] Cori G T Cori, C F., and Schmidt G J Biol Chem. 129: 629 1939

reactions, which is believed to occur, with relatively minor modifications, in widely divergent types of cells, and which may serve as a model of the manner in which glucose is catabolized[5]

from Glycogen — from Glucose — P represents $PO(OH)_2$

Glucose-1 phosphate ⇌ Glucose 6 phosphate ⇌ Fructose 6 phosphate ⇌ Fructose 1 6 diphosphate ⇌

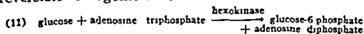
⇌ Triose phosphate {d hydroxy acetone phosphate + glyceraldehyde 3 phosphate} ⇌ 1 3 d phospho glyceraldehyde ⇌ 1 3 d phospho glyceric acid ⇌ 3 phospho glyceric acid ⇌

⇌ 2 phospho glyceric acid ⇌ phospho pyruvic acid ⇌ (enol) pyruvic acid ⇌ (keto) pyruvic acid ⇌ Lactic acid

To (Fig IV)

Fig 3—The pathway of anaerobic glycolysis

The first step in the series (fig 3) appears to be the formation of glucose 6 phosphate from glucose by the irreversible exergonic reaction



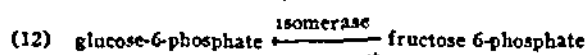
(11) glucose + adenosine triphosphate $\xrightarrow{\text{hexokinase}}$ glucose-6 phosphate + adenosine diphosphate

It should be particularly noted that this reaction is not the reversal of the reaction whereby glucose 6-phos-

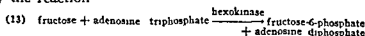
5 Barron E S G in Nord F F and Werkman C H Advances in Enzymology New York Interscience Publishers Inc 1943 vol 3 p 149 Krebs, H A. ibid 1943 vol. 3 p 191

phate is hydrolyzed to glucose (reaction 8) The enzyme catalyzing the present reaction, in contrast to the phosphatase mentioned previously, appears to be ubiquitous, and thus the hexokinase reaction would seem to occur in essentially all living cells An important consequence of this reaction is that it converts the freely diffusing glucose into a phosphate which crosses membranes with difficulty and is thereby pictured as serving to capture glucose molecules in the intracellular compartment[6] It has been suggested that it is by virtue of this mechanism of capture of glucose that the cells of the mammalian body are able to thrive on a predominantly glucose nutrient in spite of the fact that the concentration of glucose in the extracellular space is relatively low in the neighborhood of 0 1 per cent

Three possible fates of glucose 6 phosphate must next be considered In the liver but not in muscle, it may be hydrolyzed back to glucose by the action of phosphatase (reaction 8) Again by the reversal of reaction 10 it may be transformed into glucose 1 phosphate and from this product a wide variety of cells are able to form glycogen This latter reaction has been shown to require the same phosphorylase which was involved in the breakdown of glycogen (reaction 9) and in addition, a small seed of glycogen or some similar polysaccharide to initiate the coupling of one glucose fragment to another In the course of this reaction phosphate ion is eliminated The third fate of glucose 6-phosphate is its transformation to fructose 6-phosphate in the number 1 position by the reaction

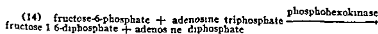


and since the same product may arise from fructose, by the reaction



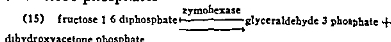
it may be considered that it is at this point that the metabolisms of glucose and of fructose merge

Fructose 6 phosphate now acquires a second phosphate in the number 1 position by the reaction

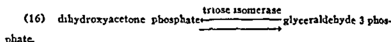


6 Soskin S and Levine R Carbohydrate Metabolism Chicago University of Chicago Press 1946

and the resulting product, loaded at both ends, undergoes cleavage at the midpoint to yield a mixture of the two triose phosphates



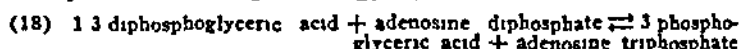
These two isomeric compounds form an equilibrium mixture in that they are biologically interconvertible



Glyceraldehyde 3 phosphate next undergoes spontaneous reaction with inorganic phosphate to yield glyceraldehyde 1,3 diphosphate It should be noted that the phosphate bond thus established is of the low energy variety (see table) When this compound is oxidized by the transfer of hydrogen to coenzyme I

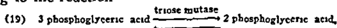


the phosphate in position 1 is transformed from a low energy phosphoric acid acetal into a high energy mixed anhydride of phosphoric acid (see table), capable of delivery to other high energy systems

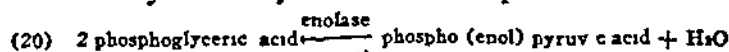


The last three reactions have in effect augmented the energy level of inorganic phosphate initially zero, up to an energy level sufficiently high to permit of the regeneration of high energy adenosine triphosphate, the energy in this case derived from the energy of oxidation of an aldehyde up to the level of a carboxy acid

The rearrangement of 3 phosphoglyceric acid according to the reaction



is followed by the dehydration of this product



In this reaction once again one sees the augmentation of energy level in a phosphate bond In the starting material, phosphate occurs as an ester of a secondary alcohol at low energy level, whereas in the product phosphate is present as a high energy enol ester (see

table) The regeneration of another mol of adenosine triphosphate is thus made possible at the expense of the energy yielded by glycosis, as is seen in the next reaction of the series

(21) phosphopyruvic acid + adenosine diphosphate ⇄ pyruvic acid + adenosine triphosphate

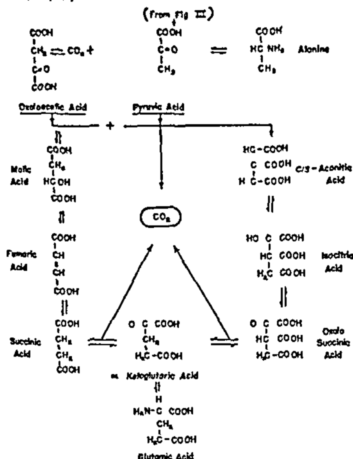
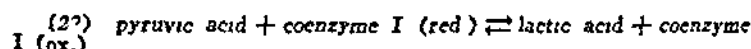


Fig 4—The oxidation of pyruvic acid.

The possible fates of pyruvic acid (fig 4) which in alkaline solution, exists as an equilibrium mixture of the enol and keto forms, are several[7] Under conditions of oxygen lack, when the several coenzymes of

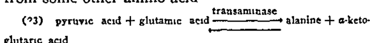
7 Stotz E in Nord F F, and Werkman C H Advances in Enzymology New York, Interscience Publishers Inc 1945 vol 5 p 129 Ochoa S Ann New York Acad Sc 47 835 1947

the hydrogen transport system are largely in the reduced state, the reaction


(22) *pyruvic acid + coenzyme I (red.)* ⇄ *lactic acid + coenzyme I (ox.)*

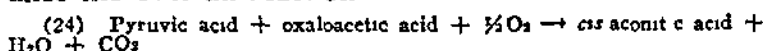
may be expected to proceed to the right to an appreciable extent and in these circumstances since lactic acid appears to have no pathway open to it other than excretion or reoxidation to pyruvic acid lactic acid may be expected to accumulate in the body fluids It may be pointed out that lactic acid ($C_3H_6O_3$) is grossly at the same level of oxidation as glucose ($C_6H_{12}O_6$) and that in the reactions described thus far there is neither an over-all consumption of oxygen nor a liberation of carbon dioxide In fact, all these reactions do run in many circumstances completely anaerobically, lactic acid accumulating as glucose disappears *In general, however, when oxygen is abundantly supplied, pyruvic acid is drained into other channels and the equilibrium* of reaction 22 is shifted to the left

Another possible disposition of pyruvic acid is its conversion to alanine by the transfer of an amino group from some other amino acid


(23) pyruvic acid + glutamic acid $\underset{\longleftarrow}{\xrightarrow{\text{transaminase}}}$ alanine + α-keto-glutaric acid

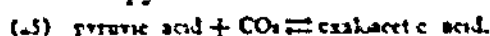
a reaction for which pyridoxal phosphate has been shown to serve as a coenzyme

Yet another fate of pyruvic acid is today supposed to entail a preliminary degradation to an as yet unidentified two-carbon fragment sometimes referred to as 'acetyl" and condensation of this product with oxaloacetic acid to yield *cis* aconitic acid In order to balance the over all reaction


(24) Pyruvic acid + oxaloacetic acid + ½O_2 → *cis* aconitic acid + H_2O + CO_2

it will be noted that oxygen is required among the reactants and carbon dioxide occurs among the products This reaction which initiates the so called 'tricarboxylic acid cycle may be taken as the first individual reaction which is necessarily aerobic A coenzyme necessary for this and indeed several other reactions of pyruvic acid is thiamine pyrophosphate and the increase in blood and urine pyruvate levels in thiamine deficient states has been ascribed to inhibition of this reaction It is noteworthy that the other reagent required for this

disposition of pyruvic acid oxaloacetic acid may in turn arise from pyruvic acid



The hydration of *cis* aconitate



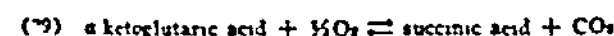
is followed by its dehydrogenation



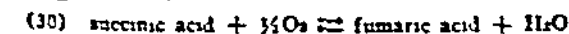
and here again to balance the over-all reaction oxygen is required Oxalosuccinic acid now undergoes decarboxylation

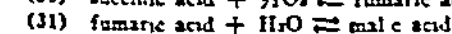


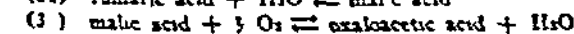
eliminating a second mol of carbon dioxide The α ketoglutaric acid thus formed may by acceptance of an amino group be transformed into glutamic acid It may, on the other hand undergo oxidative decarboxylation



Three mols of carbon dioxide have now been eliminated corresponding to the three carbon atoms of the pyruvic acid with which this the aerobic phase was initiated The remaining reactions of the cycle now called the dicarboxylic acid cycle' may be pictured as serving to regenerate, from succinic acid oxaloacetic acid







Oxaloacetic acid is thus conserved and may react with another molecule of pyruvic acid in a cyclic fashion It may, in addition accept an amino group to yield aspartic acid Three of the keto acids which arise in the course of glucose catabolism pyruvic α ketoglutaric and oxaloacetic may readily and reversibly be converted into amino acids and in this fashion a fusion of the metabolic pathways of proteins and carbohydrates is effected At some point as yet undefined in the series below pyruvic acid probably at the level of the two-carbon acetyl fragment a similar fusion of pathways of carbohydrate and fatty acid metabolism occurs whereby the over all conversion of glucose to fatty acid takes place on the one hand and the products of fatty acid degradation feed into the tricarboxylic acid cycle on the other

Perhaps the most striking fact about this series of reactions is the occurrence of numerous individual steps whereby energy is released in small packages rather than all at once in an explosive fashion This gradual release of energy permits of its more efficient utilization in the endergonic processes of the body and certain of the energy links that occur as glucose is degraded to pyruvate have been described It should be pointed out, however, that the yield in energy as glucose is converted to pyruvate is far less than the yield obtained when pyruvate is further degraded to carbon dioxide and of the energy links operating in this the oxidative phase, little is known

MAINTENANCE OF BLOOD GLUCOSE

For the cells of the body to carry out these reactions on glucose a certain minimum concentration of glucose in the extracellular fluid must be maintained One of the important mechanisms operating in this direction is the kidney which normally prevents the loss of significant quantities of glucose in the urine as long as the level of blood glucose is below the threshold value This is accomplished by the more or less quantitative reabsorption of glucose from the glomerular filtrate, a process in which the tubule cells transport at least a portion of the glucose against a concentration gradient Such transport cannot be accounted for on the basis of simple diffusion and necessarily consumes energy, and in view of the fact that such 'up-hill' transport of glucose operates not only at the renal tubule but also at the intestinal mucosa and possibly elsewhere, it may be well to consider whence the necessary energy may arise The sequence of events may be pictured as follows Glucose diffuses across the barrier separating the lumen from the contents of the tubule cell once in the cell it is phosphorylated according to reaction 11 which in effect disturbs the equilibrium in favor of diffusion of glucose into the cell from the lumen Whereas glucose 6 phosphate does not escape from the cell it may be pictured as circulating in the cytoplasm of the cell and coming in contact with a phosphatase which effects an irreversible hydrolysis according to reaction 8 A high concentration of glucose may thus be built up locally and glucose may then diffuse from the intracellular fluid into the blood stream To compute the energy which would be expended by

such a sequence of events, one has merely to add reactions 8 and 11, the sum being

(33) adenosine triphosphate → adenosine diphosphate + inorganic phosphate

In other words, to transport one molecule of glucose against a concentration gradient by this means entails the loss of one high energy phosphate bond That some such mechanism is operating at the renal tubule is indicated by the fact that phlorhizin, a known poison of phosphorylating systems, decidedly inhibits the tubular reabsorption of glucose

Factors other than renal activity which serve to maintain the blood glucose at normal levels may conveniently be considered with reference to the endocrines which control these factors Thus, the effect of epinephrine on carbohydrate metabolism may be assigned to an enhancement of the conversion of glycogen to glucose-6 phosphate (reactions 9 and 10) In the well nourished animal with ample hepatic glycogen the major effect observed is a decrease in the quantity of glycogen of the liver and an increase in the quantity of blood glucose arising from the ready hydrolysis of glucose-6-phosphate in the liver (reaction 8) In the previously fasted animal however in which the glycogen of the liver is depleted, the injection of epinephrine is followed by a decrease in glycogen of the muscle At this site, however glucose 6-phosphate cannot be hydrolyzed and the glucose-6-phosphate therefore follows the path of anaerobic glycolysis (reactions 12 through 22) and the resulting lactic acid escapes into the bloodstream The depleted liver captures a fraction of this lactic acid which it may then convert into glycogen

The anterior pituitary gland produces a specific inhibitor of the enzyme hexokinase (reaction 11)[8] It appears to operate predominantly on the hexokinase of muscle and liver cells and has little or no effect on the hexokinase contained in the cells of the central nervous system the renal tubule or the intestinal mucosa Since the hexokinase catalyzed phosphorylation of glucose is in a sense a key reaction in the utilization of glucose the presence of an excess of this

[8] Cori, C F in The Harvey Lectures 1945 1946 Lancaster Pa. Science Press Printing Company 1946 vol. 41 p 253

inhibitor would be expected to interfere with the utilization of glucose especially in muscle and in liver A retardation in the formation of glucose 6-phosphate at these sites will result in an impairment of the utilization of glucose by these tissues as well as a decrease in the formation of all the substances which these tissues normally generate from glucose, among others lactic and pyruvic acids, glycogen, fatty acids and carbon dioxide

One of the actions of the secretion of the adrenal cortex appears to be an enhancement and prolongation of the action of this pituitary hexokinase inhibitor When present in excess, essentially the same effects on the utilization of glucose by muscle and liver may be anticipated The oxygenated steroids of the adrenal cortex are believed to have another effect on carbohydrate metabolism namely they are supposed to favor gluconeogenesis at the expense of glucogenic amino acids of the proteins of the body Both of these actions of the adrenal cortex will operate to increase the level of blood glucose, the one by impeding utilization and the other by favoring glucose synthesis

An important action of insulin lies in its antagonism to the action of the inhibitor of hexokinase Whereas insulin has no effect on hexokinase itself it does serve to release this enzyme from the inhibition imposed on it by the anterior pituitary and the adrenal cortex Assuming hexokinase in the normal animal to be continuously moderately inhibited the action of insulin would be to remove this inhibition and thus indirectly to stimulate the enzyme The phosphorylation of glucose would then proceed more rapidly, glucose would disappear from the extracellular compartment glucose-6-phosphate would be formed in abundance in muscle and liver cells and products derived from glucose 6 phosphate would secondarily be formed at greater than normal rates Essentially all of these effects have been observed to follow the administration of insulin Insulin lack on the other hand would be expected to simulate chemically the picture described as following the presence of an excess of hexokinase inhibitor This picture is in fact a good description of the biochemical defect in diabetes mellitus [9]

9 Stetten DeW Jr Endocrine Regulation of Carbohydrate Metabolism, J A M A 132 373 (Oct 19) 1946

The release of insulin by the cells of the islets of Langerhans appears itself to be dependent on the level of blood glucose, the higher the blood glucose, the more insulin discharged This mechanism is subject to exhaustion, however, and prolonged maintenance of the blood glucose at an excessively high level is followed in certain species, by irreversible injury to the islets and the picture of permanent diabetes [10]

In the adult normal animal in balance and at constant weight the glucose made available by the various processes that have been described must be equal to the glucose that is being consumed in the several processes outlined The magnitudes of these several processes in human beings have not been exhaustively studied In the rat it would appear that about one third of the glucose is used in the elaboration of fatty acids which are needed to replenish the fat stores of the body, and only about one thirtieth is required for the maintenance of the glycogen reserves The remainder is presumed to be degraded ultimately to carbon dioxide and to contribute carbon atoms along the way to other compounds which the body may synthesize from such fragments

There is no specific nutritional deficiency related to the lack of glucose in the diet However it has long been recognized that when for any reason the rate of utilization of glucose is subnormal there is a likelihood of the development of ketonemia and ketonuria This may arise as a result of deprivation of dietary glucose diabetes or renal glycosuria and may in general be rectified by the reestablishment, by suitable procedures of normal glucose catabolism This action of glucose, its so-called antiketogenic' action is today fairly well understood The ketone bodies are not abnormal metabolites but are formed normally and abundantly in the course of fatty acid degradation probably chiefly in the liver They do not accumulate in the blood of the normal person because they are normally consumed in muscle and liver as rapidly as they are formed Only when they are produced in excessively large amounts do clinical ketonemia and ketonuria develop and this is undoubtedly what happens when, for one reason or another glucose is not being utilized at the proper rate When glucose is

10 Dohan F C and Lukens F D W Science 105:183 1947

scarce, either because of lack of dietary carbohydrate or because of loss of glucose in the urine or when glucose, though abundantly present is not being catabolized at a normal rate, excessive quantities of fat are transported from the depots to the liver and there degraded, probably to two-carbon "acetyl" fragments and a portion of these are converted into acetoacetic acid If these normal processes become sufficiently exaggerated, the rate of acetoacetic acid formation will exceed the body's capacity to destroy this compound and its level in the blood will rise The reestablishment of carbohydrate metabolism in such a subject appears to relieve the liver of the necessity of degrading fatty acids at excessive rates and as the formation of ketone bodies resumes its normal rate, the ketone bodies which had accumulated in the body are either excreted in the urine or destroyed by the tissues of the body in their normal fashion It may be noted in passing that acetoacetic acid and "acetyl" with which it is interconvertible, are believed to be catabolized by initial condensation with oxaloacetic acid to yield the same *cis* aconitic acid encountered in the breakdown of glucose (reaction 24) From this point on the breakdown of acetyl, derived from fatty acids and of pyruvate derived from glucose apparently follow identical pathways

FUSION OF METABOLIC PROCESSES

From the foregoing discussion it will be apparent that the catabolic pathways of the carbohydrates fats and proteins cross at many points and that within wide limits one nutrient may be substituted for another without significant injury to the metabolizing tissue Each of the three major classes of nutrients may supply organic fragments which feed into the tricarboxylic acid cycle a sequence of reactions which apparently serves to supply a large portion of the energy need of many biologic systems As this fusion of metabolic pathways has been elucidated the classic lines of demarcation between the metabolisms of fat protein and carbohydrate have become progressively more obscure and more meaningless The picture that is developing is one of reaction sequences often cyclic which liberate energy as needed by the organism and these cycles apparently may be fed at many points and in many ways Although extreme deviation from the normal composi

tion of the nutrient mixture may result in the undue accumulation of one or another intermediate a considerable degree of variation is tolerated Whereas the catabolic breakdown of protein fat and carbohydrate will undoubtedly continue to be taught, for purposes of convenience as separate entities the better understanding of these processes is leading to a more highly integrated point of view

The present bibliography has been limited to a few selected papers and reviews of general interest. No attempt has been made to justify each statement in the text by citation from literature For a more complete discussion and bibliography the reader is referred to Peters, J P., and Van Slyke, D D Quantitative Clinical Chemistry ed. 2, Baltimore Williams & Wilkins Company 1946 vol. 1 chap 1-4

CHAPTER IV

HUMAN REQUIREMENT OF CALCIUM, PHOSPHORUS AND MAGNESIUM

GENEVIEVE STEARNS

Calcium phosphorus and magnesium are usually considered together, from a nutritional point of view, because all three occur in bone, and, with carbonate, make up the major part of the bone mineral The metabolic paths of the three elements are by no means wholly parallel even though the major part of the body content of each is found in the same tissue Whereas 99 per cent of body calcium is found in the skeletal structures, bones and teeth, both phosphorus and magnesium are important constituents of soft tissue also The small amount of calcium not in bone is a component of extracellular fluid magnesium and phosphate on the other hand are components of intracellular fluids, and the phosphate radical appears to be essential in an ever increasing number of metabolic reactions

Milk and its derivatives, such as cheese and ice cream are the chief sources of calcium in the diet and provide ample phosphorus for its utilization Other protein rich foods, as meat eggs fish cereals and legumes contribute much phosphorus and a considerable percentage of the daily magnesium intake but add little or no calcium to the diet The acidity of many fruits is in part due to acid phosphates

Foods containing oxalic or benzoic acids, as spinach, beet greens and cranberries, decrease the absorption of calcium and magnesium as the oxalates and benzoates of these minerals are insoluble A high ratio of phosphorus to calcium and magnesium in the diet also depresses their absorption as these phosphates are less soluble in the presence of an excess of phosphate

From the Department of Pediatrics, College of Medicine State University of Iowa

ion The phosphorus of whole grain cereals is largely in the form of phytin Calcium and magnesium phytates are highly insoluble so the ingestion of phytin usually results in the loss of its own phosphorus together with calcium and magnesium supplied by other foods except as vitamin D makes some of the phytin phosphorus available As the calcium is more apt to be in short supply than is dietary phosphorus, countries using whole grain flour often add calcium carbonate in sufficient quantity to compensate for the phytin content of the flour [1]

With the dietary patterns common to this country dietary deficiency of phosphorus is unlikely, deficiency of calcium is common

In order to understand the factors determining the daily requirement of these elements a brief resume of the intermediary metabolism of each is presented

CALCIUM

The intermediary metabolism of calcium is schematically represented in figure 1 The amount actually available to the body is the amount absorbed from the gastrointestinal tract To be absorbed the calcium salt must be in solution Calcium salts, as they occur in foods, are not easily soluble in neutral or alkaline solution Their absorption, therefore occurs largely in the upper part of the small intestine while its contents are still somewhat acid Calcium absorption will thus depend in considerable measure on the maintenance of a normal gastric acidity Vitamin D increases the amount of calcium absorbed from the small intestine [2] though the mechanism of its action is not fully understood The ingestion of lactose and especially of protein [3] are known also to increase the absorption of calcium On the other hand calcium salts of fatty acids the calcium soaps are highly

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1 McCance R. A and Widdowson E. M Mineral Metabolism Ann. Rev Biochem 13 315 1944

2 (a) Nicolaysen R Studies upon the Mode of Action of Vitamin D II The Influence of Vitamin D on the Faecal Output of Endogenous Calcium and Phosphoru in the Rat III The Influence of Vitamin D on the Absorption of Calcium and Phosphorus in the Rat, Biochem J 31 107 and 12? 1937 (b) Untersuchung uber die Kalk ausscheidung bei Hunden Skandinav Arch. f Physiol. (supp) 69: 1 1934 (c) Nicolaysen R and Jansen J Vitamin D and Bone Formation in Rats Acta paediat. 23 405 1939

3 McCance, R A Widdowson E. M and Lehmann H The Effect of Protein Intake on Absorption of Calcium and Magnesium, Biochem. J 36 686 (Sept.) 1942.

insoluble, as are oxalates, benzoates and phytates These are precipitated in neutral or alkaline mediums

Regardless of intake, calcium is never completely absorbed Food calcium is not the only source of calcium entering the gastrointestinal tract The amount of calcium entering the tract as a component of digestive secretions seems to be little appreciated but is of very real importance According to Gamble[4] the volume of digestive secretions produced each 24 hours by an adult of average size averages 8 200 ml, or over 2 3 times the mean plasma volume of 3 500 ml Logan[5]

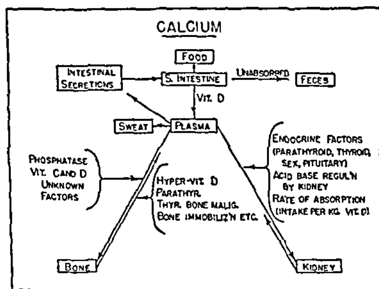


Fig 1—Schematic representation of the metabolism of calcium.

places the range of volume of digestive secretions at 4 000 to 10,000 ml The amount of calcium in these secretions varies from 5 to 10 mg per 100 ml[2b] and averages approximately 8 mg per 100 ml Thus from 0 3 to 0 8 Gm, with a mean of about 0 65 Gm of calcium is secreted into the gastrointestinal tract daily Many adults ingest much less than 0 8 Gm of calcium a day If conditions in the tract do not favor absorption, much of the calcium of the digestive secretions as

4 Gamble J L. Chemical Anatomy Physiology and Pathology of Extracellular Fluid Cambridge Massachusetts Harvard University Press 1947

5 Logan M A Recent Advances in the Chemistry of Calcification, Physiol. Rev 20:522 (Oct.) 1940

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1 McCance R. A and Widdowson, E. M Mineral Metabolism. Ann. Rev Biochem **13** 315 1944

2 (*a*) Nicolaysen, R Studies upon the Mode of Action of Vitamin D II The Influence of Vitamin D on the Faecal Output of Endogenous Calcium and Phosphorus in the Rat III The Influence of Vitamin D on the Absorption of Calcium and Phosphorus in the Rat, Biochem J **31** 107 and 122 1937 (*b*) Untersuchung uber die Kalk ausscheidung bei Hunden Skandinav Arch f Physiol. (supp) **69** 1 1934 (*c*) Nicolaysen R and Jansen, J Vitamin D and Bone Formation in Rats Acta paediat. **23** 405 1939

3 McCance *R A Widdowson E. M and Lehmann H The Effect* of Protein Intake on Absorption of Calcium and Magnesium, Biochem. J **36**: 686 (Sept.) 1942.

The factors governing deposition of mineral in teeth are presumably similar to those affecting its deposition in bone Studies of radioactive phosphorus show that the metabolic rate of teeth is considerably slower than that of bone, the rate of "turnover," that is, deposition and withdrawal of mineral from enamel is extremely slow The biochemistry of teeth has been recently reviewed by Leicester [11]

Removal of mineral from bone is dependent, at least in large part on the activity of the parathyroid hormone which maintains serum calcium at a constant level using bone as a reservoir In certain circumstances mineral is removed from bone more rapidly than it is deposited resulting in osteoporosis Such removal may be limited to one bone only because of immobilization of that bone or to disease affecting one bone only Often the demineralization is general and very gradual as for example the osteoporosis of middle or old age which is probably the result of several factors, as poor circulation due to decreased exercise atrophy of bone matrix or ingestion of a calcium intake insufficient to permit replacement of normal loss The effect of a long-continued low calcium intake will be aggravated if the customary diet is acid in ash requiring additional body base for neutralization More rapid and general loss of bone mineral occurs with the production of excessive amounts of acid in the body or with an excessive production of parathyroid or thyroid hormone Excessive intake of vitamin D or dihydrotachysterol likewise results in an outpouring of mineral from bone

The factors influencing excretion of calcium in urine have been carefully studied by Knapp [12] These include the quantity of calcium intake the skeletal size the acid base regulation of the body and especially the endogenous factor(s) assumed to be the resultant of various body hormones chiefly those of the parathyroid and thyroid but also including to a lesser degree the sex and pituitary hormones Probably because of these endogenous factors the normal range of variation of urinary calcium is far wider than is

11 Leicester H M The Biochemistry of Teeth, St Louis C V Mosby Company 1949

12 Knapp E L Factors Influencing the Excretion of Calcium in Normal Persons J Clin. Investigation 26: 182 (March) 1947

well as that of the food will be excreted Hence, particularly when the calcium intake is low fecal excretion may greatly exceed intake

Calcium is absorbed directly into the plasma, where it is maintained at a level of approximately 10 mg per 100 ml largely through the action of the parathyroid hormone The level of plasma calcium also tends to vary in the same direction as the serum protein and inversely as the serum inorganic phosphorus About half the plasma calcium is in ionized form Calcium is distributed through the other extracellular fluids of the body in amounts decreasing with the protein content of the given fluids Cerebrospinal fluid contains only 5 to 6 mg per 100 ml

Other than the small but important amount of calcium remaining in extracellular fluids of the body, absorbed calcium is quickly deposited in bone The process of deposition of mineral in bone is complicated and not fully understood The physicochemical laws of precipitation of salts from solution are insufficient to explain the process A phosphatase active in alkaline medium[6] and possibly other enzymes are concerned Considerable evidence points toward vitamin D as a factor in calcification of bone as well as in absorption of calcium[7] The importance of vitamin C has been demonstrated for the calcification process as well as for the integrity of the matrix[8] still other factors are postulated Other authors have discussed more fully the factors involved in the mineralization of bones and teeth[9]

Calcium and phosphorus are deposited first in the epiphysis of growing bone and thence transferred to the diaphysis from which they are removed slowly according to studies using radioactive isotopes[10] New mineral *is deposited to replace that removed*

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6 Robison, R The Significance of Phosphoric Esters in Metabolism New York The New York University Press 193

7 Greenberg D M Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes J Biol. Chem. **157** 99 (Jan) 1945

8 Bourne G Some Experiments on th Possible Relationship Between Vitamin C and Calcification *J Physiol.* ***102*** *319 1943*

9 (*a*) Logan. (*b*) Sobel A. E Rockenmacher M and Kramer B Composition of Bone in Relation to Blood and Diet J Biol Chem **159** 1 9 (June) 1945 (*c*) Manly M L. and Bale W F The Metabolism of Inorganic Phosphorus of Rat Bones and Teeth as Indicated by the Radioactive Isotope, J Biol Chem **129** 1 5 (July) 1939 (*d*) Greenberg D M Mineral Metabolism Calcium Magnesium and Phosphorus Ann Rev Biochem. **8** 269 1939 (*e*) Hevesy G Application of Radioactive Indicators in Biology *Ann. Rev Biochem* ***9*** *64 1940* (*f*) *McLean* F C. Physiology of Bone Ann Rev Physiol. **3** 79 1943 (*g*) Sendroy J Jr Mineral Metabolism Ann. Rev Biochem. **14** 407 1945

10 Greenberg[7] Hevesy[9e]

intake is absorbed than is true for calcium, and the fecal excretion is a correspondingly smaller percentage of intake

All body phosphorus exists as orthophosphate either in organic or inorganic combination In the blood stream, inorganic phosphate is carried in plasma, lecithin in both plasma and cells and phosphate esters (acid soluble phosphorus) almost entirely in the cells, less than 1 mg per 100 ml (as phosphorus) being found in plasma

Deposition and release of bone phosphate are under the same regulatory mechanisms as those for calcium

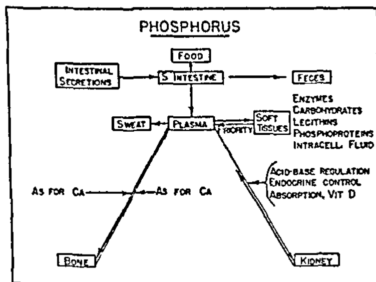


Fig 2—Schematic representation of the metabolism of phosphorus.

In fact much of the recent knowledge concerning mineral metabolism of bone has been achieved through the use of radioactive isotopes of phosphorus[14] The phosphorus of soft tissues exists as both organic and inorganic phosphate and plays a highly important part in many body processes This phase of phosphorus metabolism has been recently reviewed[15] Phosphorylation appears to be an essential step for the absorption of many nutrients, as fatty acids and hexoses The

14 Greenberg[8] Manly and Bale[9c] Hevesy[9a]
15 Kalckar H M The Chemistry and Metabolism of the Compounds of Phosphorus Ann Rev Biochem. 14:283 1945

usually appreciated, the maximum normal excretion at any level of intake per kilogram is approximately 10 times the minimum Thus if two persons are of equal size and are given the same dietary regimen one may normally excrete 25 mg of calcium daily and the other 250 mg a day Obviously the second person needs a higher intake for maintenance than does the first

McCance and Widdowson[13] have observed that in adults who are not retaining calcium, the urinary calcium increases with increase in calcium absorption, in children such rise in urinary calcium does not often occur, for increased calcium absorption results rather in increased retention[12]

Ordinarily the amount of calcium excreted in sweat is very small and is usually disregarded in a study of calcium retention

To summarize, in the normal person the factors which appear most important in regulating the ability of the body to absorb and retain calcium are the maintenance of a normal gastric acidity the maintenance of an adequate supply of vitamin D, either by ingestion or by manufacture within the body the maintenance of a calcium intake sufficiently large to allow for both the inevitable loss of calcium through its precipitation as insoluble salts in the intestine and the urinary calcium excretion peculiar to the individual subject It is not *surprising from the foregoing material, that the* requirement for calcium may vary rather widely from person to person and even in the same person at different times

PHOSPHORUS

The intermediary metabolism of phosphorus is indicated schematically in figure 2 In many respects the metabolism of phosphorus follows that of calcium however, more of the body phosphorus, between 10 and 20 per cent is found in tissues other than bone and the phosphorus of soft tissues seems to have metabolic priority over that of bone

The intake of phosphorus usually exceeds that of calcium, except in infants and small children whose diet is predominantly milk A far greater percentage of

13 McCance R A and Widdowson E M Significance of Urinary Calcium, Phosphorus and Magnesium J Physiol. 101: 350 (Nov) 1942.

have been less satisfactory Magnesium occurs in meats cereals, other plant foods and milk Magnesium salts are similar to those of calcium in solubility, probably the same factors govern the absorption of both[21]

In general the intermediary metabolism of magnesium resembles that of phosphorus in that magnesium is a component of soft tissues as well as of bone Potassium and magnesium are the cations of intracellular fluid Magnesium is a component of certain organic complexes notably those containing members of the B group vitamins and appears to catalyze certain enzyme reactions, as phosphatase

The factors regulating the deposition of magnesium in bone and its withdrawal have been most thoroughly studied by Duckworth and Godden[22] According to these investigators the skeletal magnesium is highly labile and forms a reserve easily drawn on by soft tissues which appear to have priority The return of magnesium to bone after depletion is a slower process than its removal[1] Deficiency of magnesium disturbs calcium metabolism, in calcium deficiency, when magnesium is available magnesium can replace calcium of bone to a limited extent Although the amount of magnesium in blood plasma is normally small 1 to 3 mg per 100 ml, magnesium tetany has been observed in young animals and is reported to have occurred in a child[23]

DAILY REQUIREMENT OF CALCIUM PHOSPHORUS AND MAGNESIUM

General—From the foregoing discussion it will be evident that the minimum requirement of any of these less soluble elements will depend in considerable degree on the state of health of the person particularly on his efficiency of absorption It appears almost axiomatic that if the dietary regimen is adequate in all respects and the subject is in excellent health, the efficiency of absorption will be maximum if the diet is incomplete

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21 Duckworth J and Warnock G W The Magnesium Requirements of Man in Relation to Calcium Requirements with Observations on the Adequacy of Diets in Common Use Nutrition Abstr & Rev **12**: 167 194 *1943*

22 (*a*) Hevesy[84] (*b*) Duckworth J and Godden W Replenishment of Depleted Skeletal Reserves of Magnesium Biochem J **37**: 595 1943

23 Miller J F Tetany Due to Deficiency in Magnesium Occurrence in a Child of Six Years with Associated Osteochondritis of Capital Epiphysis of Femur (Legg Perthes Disease) Am J Dis. Child. **67**: 117 (Feb) 1944

phosphate radical is bound to proteins, fatty acids carbohydrates and enzymes High energy phosphate bonds permit gradual release of energy during the oxidation of glycogen in muscle The phosphate ion is the chief inorganic anion of intracellular fluids *Phosphates of extracellular fluids are useful in the* regulation of the acid base balance of the body for the excretion of acid phosphate in urine is one of the means of maintaining acid-base balance in the body although the relationship may not be as direct as it has been considered to be [16]

The effect of vitamin D on the intermediary phosphorus metabolism differs somewhat from its effect on the metabolism of calcium whereas vitamin D increases the absorption of calcium from the intestine its effect on the absorption of phosphorus is negligible [2] Administration of vitamin D appears, however, to hasten the transfer of organic phosphate of the soft tissues to inorganic phosphate available for deposition in bone [17] Vitamin D increases the rate of reabsorption of phosphorus from the renal tubules [18] which may explain its effect on the serum phosphate and on calcification in rickets

Parathyroid hormone administered to normal animals tends to increase the urinary excretion of phosphorus somewhat earlier than that of calcium [19] Some observers have felt that a decrease in tubule reabsorption of phosphate, was the chief effect of parathyroid hormone These conclusions have recently been challenged [20] and the chief effect of the parathyroid hormone on the kidney is considered to be an increase in reabsorption of calcium with no alteration in rate of reabsorption of phosphorus

MAGNESIUM

The metabolism of magnesium has been studied far less thoroughly than that of calcium or phosphorus partly because chemical methods for its determination

16 Pitts R. F and Alexander R S Th Renal Reabsorptive Mechanism for Inorgan c Phospho us in Normal and Ac d t c Dogs Am J Physiol **142** 648 1944

17 Cohn E W and Greenberg D M Studies in Mineral Metabolism with the A d of Art fic al Rad oactive Isotopes I Ab o pt on D stribution and Excret on of Phosphorus J Biol Ch m **123**: 185 (M rch) 1938

18 Harr son H E and Ha r son H C Th Renal Excret on of Inorgan c Phosphate in Relation to the Act on of V tam n D and Parathyroid Hormone J Clin. Investigat on **20** 47 1941

19 Harrison and Harrison Tw edy W R and Campbell W W The Effect of Parathyro d Extract Upon the D tribut on R tent on and Excretion of Labeled Pho phorus J Biol Chem **154** 339 1944

20 Jaban I and Pitts R F Am. J Phys ol. **155**: 42 (Oct.) 1948

some degree of osteoporosis in adults[26] Estimations of quantity of calcium theoretically contained in a completely mineralized skeleton have varied from 1,000 to 2,000 Gm The daily retention considered as needed at any age during growth will vary considerably depending on the total accepted as standard

Sufficient data on actual retention of calcium at various ages have now been published to establish the fact that the calcium retention from a given intake tends to vary with the rate of growth common for the age of the child Thus the correctness of the principle involved may be considered as established Strangely, the quantity of retention from a given intake appears to vary with growth in weight rather than growth in height of the child [26b] Actual retention of calcium by healthy normal children given ample amounts of this element usually is well above the minimal amount calculated as necessary for the age Thus either the well fed child maintains a better mineralized skeleton than necessary to provide an adult skeleton of calcium content similar to the skeletons analyzed or the withdrawals of calcium from the skeleton are sufficiently numerous and severe that allowance for such withdrawal should be made in setting the requirement It seems probable that both factors are involved

During those periods of life in which milk is the chief food the intake and relative proportions of calcium, phosphorus and magnesium in the diet are assumed adequate Human milk provides for good growth and development of the full term infant The calcium and phosphorus of human milk average 320 and 130 mg per liter, compared with 1,180 and 930 mg respectively for calcium and phosphorus of cow s milk[27] The ratio of calcium to phosphorus in human milk is close to that in bone the low protein content of human milk provides for a relatively slow increment of body tissue, so that the phosphorus intake is adequate Only traces of phosphorus may be excreted in the urine of these infants demonstrating that the margin of adequacy of phosphorus intake is narrow The absorption of both calcium and phosphorus is excellent—50 to 70 per cent

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26 (a) Gilbert A and Posternak S Über die Phosphortherapie Vom Standpunkt des Stoffwechsels aus betrachtet Artzliche Rundschau **15**: 398 1905 (b) Mitchell H H Hamilton T S Steggerda F R and Bean H W The Chemical Composition of the Adult Human Body and Its Bearing on the Biochemistry of Growth J Biol. Chem **158** 6?5 (May) 1945

27 Jeans, P C and Marriott, W McK. Infant Nutrition ed 4 St. Louis C V Mosby & Company 1947 p 158

in one or more essentials, the efficiency of the gastro intestinal tract will be lessened and a larger percentage of these minerals may be unabsorbed

Illness, particularly febrile illness, is accompanied with decrease in gastric acidity and a decreased absorption of calcium [24] and probably, also, of magnesium and phosphorus Return to normal efficiency of the gastro intestinal tract may be slow, low grade chronic upper respiratory infections or recurrent colds definitely decrease the absorption of calcium in infants and small children for periods of weeks or months [24b] Allowance for such periods often must be made in setting daily requirements for any given dietary essential

Calcium —As factors affecting the utilization of one of the three elements discussed tend to affect the utilization of all, and as the requirement of calcium has been more fully studied than those of phosphorus and magnesium, the major part of this discussion is necessarily devoted to calcium requirement

Several excellent reviews of calcium metabolism with particular reference to requirement have been published [25] There seems no further need for detailed discussion of various reported studies of calcium metabolism or for elaboration on the separate conclusions of the various reviewers

It is generally agreed by all investigators that the calcium requirement during growth must be based on skeletal need as 99 per cent of body calcium is in the skeleton Estimation of skeletal need is based on the calcium content of the adult skeleton divided according to the proportionate rate of growth during each year of the growth period Differences of opinion have arisen over whether the actual calcium content of the two adult skeletons analyzed should be considered as the standard for calcium content despite complete lack of nutritional history and the well known prevalence of

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24 (*a*) Malmgren N Ueber Den Stoffwechsel des Gesunden Naturlich Ernahrten Saugl ngs und dessen Beeinflussung durch parenteral Infektion und Intoxication Acta paediat. 2 209 1923 (*b*) Stearns, G Unpublished data

25 (*a*) Leitch I The Determ nation of the Calcium R quirements of Man Nutrit on Abstr & Rev 6 553 (Jan) 1937 (*b*) Holmes J O The Requirement of Calc um During G owth Nutrition Abstr & Rev 14: 597 (Apr l) 1945 fig 3 (*c*) Macy I G Nut tion and Chem cal Growth in Ch ldhood I Evaluat on Sp ingfield Ill Charl s C Thomas Publisher 1942 (*d*) Shohl A T Mineral Metabol sm Am. Chem Soc Monograph Series New York Rhe nhold Publi hing Company 1939 (*e*) Mitchell H H and Curzon, E G The D etary Requirement of Calcium and Its Sign ficance Paris Hermann et Cie 1939

D intake to approximately 350 I U daily results in an increase in absorption to 35 to 40 per cent of the intake, further increase in vitamin D results in no greater percentage absorption

Childhood—After the child reaches the age of walking, introduction of other foods in the diet increases to the point where the ratio of calcium to phosphorus in the diet is significantly altered Foods other than milk generally contain far more magnesium and phosphorus than calcium This change tends to increase the absorption of phosphorus at the expense of calcium absorption The question of how much milk is desirable in the day's diet becomes important

The rate of growth in height slows during the preschool years and the relative proportion of body weight due to skeletal muscle increases [32] The mineral needed daily for bone is less at this period than at any other time during growth and that for soft tissue proportionately high The requirement for magnesium and phosphorus will be relatively less diminished than the calcium requirement

Even with added vitamin D the efficiency of absorption of calcium magnesium and phosphorus is apt to decrease during this period The addition of other foods, with increase in undigestible material and the decreased intake ratio of calcium to phosphorus both tend to decrease absorption In addition and more important the number of febrile illnesses with their concomitant decrease in absorption increases sharply as the child is exposed to a wider circle of playmates For these reasons it is generally considered safer to allow an intake of 1 Gm of calcium daily [33] even though a well child receiving vitamin D and a nutritionally adequate diet will retain sufficient calcium from 1 pint (500 ml) of milk daily or a total intake of 0 7 to 0 8 Gm of calcium The additional milk provides protein which is much needed by this age group and likely to be in short supply otherwise An intake of 1 Gm of calcium daily from milk together with an otherwise adequate diet allows ample intake of magnesium and phosphorus

Children of school age also thrive and can maintain calcium retention adequate for growth and bone mineralization when given an adequate diet containing 1

32 Stearns G To be published

33 Recommended Dietary Allowances revised 1948 National Research Council Reprint and Circular Series no 129 October 1948

of the calcium and over 90 per cent of the phosphorus are absorbed, urinary excretion of calcium is small usually less than 10 mg daily The total amount of mineral absorbed daily is insufficient however to maintain the mineral content of the rapidly growing skeleton at its birth percentage [8] Many investigators, therefore, consider that the bones at birth contain an added store of mineral to permit the rapid growth of early infancy with the low ingestion of these minerals The fact that the long bones at birth are almost completely filled with cancellous bone and the marrow cavity does not become well developed until later, lends support to this storage theory [9] Certainly a breast fed infant especially if given added vitamin D, maintains good growth and development and avoids rickets even though the bones do become somewhat less well mineralized

The *prematurely born infant, who has missed the* storage of calcium that normally occurs during the last four to eight weeks of gestation, and who in addition, has a very small gastric capacity, will fare less well on human milk than his full term brother He may not be able to absorb and retain sufficient mineral to prevent rickets simply because sufficient mineral cannot be ingested from human milk [30] Many clinicians add powdered skimmed milk to the human milk fed such an infant thus increasing protein and mineral intake Other premature infants have been satisfactorily fed with low fat cow s milk mixtures Vitamin D is necessary for the premature as for the full term infant

Infants fed cow's milk without added vitamin D absorb on the average only about 10 per cent of the calcium Absorption is also most variable and the same infant may show excessively high retention at one time and heavy loss from the body at another, with no apparent cause for the shift The addition of vitamin D increases the mean absorption and maintains it at a more consistent level [31] This increase in absorption apparently is at a decreasing rate with increasing intake of vitamin D Increase in the vitamin

28 Stearns G The Mineral Metabolism of Normal Infants Physiol Rev **19** 415 (July) 1939

29 Eliot M M and Park E A Rickets in Brennemann A System of Pediatrics Hagerstown Md W F Prior Company Inc. 1948 vol 1 chap 36 p 9

30 Stearns [28] Benjamin, H R. Gordon H H and Marples E. Calcium and Phosphorus Requirements of Premature Infants, Am. J Dis. Child **65** 412 (March) 1943

31 Stearns, G., and Jeans P C. To be published.

investigation 5 months In a second study similar subjects were given 1 quart (1,000 ml) of milk and 400 I U of vitamin D daily together with a diet adequate in all known essentials The retention of calcium and phosphorus low at first increased steadily to a maximum which was achieved in about five or six months Maximum retention was in some cases as high as 800 mg daily A third group of children who had been well fed for several years at least, prior to this study showed ample retention of calcium (400 to 500 mg daily) at all times when receiving a good diet containing 1 quart of milk and 400 I U of vitamin D daily These experiments tend to reemphasize that chronic substandard nutrition is compatible for a time with maintenance of average growth in weight and height and that recovery from such substandard nutrition is not a matter of days but of months The finding that well nourished children 11 to 14 years old, given a good diet retained larger quantities of calcium than did a poorly nourished group corroborates the finding reported by Breiter and her co workers[36] that the largest calcium retention values were shown by subjects whose diets had previously been ample These data raise considerable doubt as to the validity of the common assumption that very high retention values always indicate previous depletion and that children well nourished with respect to calcium will tend to have a lower retention of this element than ill nourished children with the same intake It seems that the most important factor in determining the utilization of minerals by young adolescents is the maintenance of a good nutritional state for several years preceding puberty

The National Research Council allowances for calcium are increased at 13 years of age from 1 Gm to 1 4 Gm of calcium daily for boys and 1 3 Gm for girls[31] Actual studies of calcium retention[25b] show that periods of greatest retention probably do not coincide with periods of greatest growth in adolescence but may precede the rapid growth by two years or more In the majority of children, the prepuberal

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36 Breite H Mills R Dwight J McKey B Armstrong W and Outhouse J The Utilization of the Calcium of Milk by Adults J Nutrition **21**: 351 (April) 1941

Gm of calcium daily[34] Growth at this period is steady and not excessively rapid The child's immunity to infection increases, resulting in fewer periods of decreased mineral absorption due to febrile illness Vitamin D is an essential, however, as it is for the younger children,[34b] and for good utilization the diet must be fully adequate in all respects

As the child approaches puberty he enters a period of nutritional stress Physical changes occur, hormones are secreted in amounts which vary widely from day to day Emotional changes are rapid and extreme and affect the production of digestive secretions vagaries of food likes and dislikes times of eating amount of sleep and amount of physical exertion all vary widely and unpredictably It is not surprising that nutritional failure may and often does occur during this period

Insufficient studies of nutritional requirements of young adolescents have been published Such studies, published and unpublished, as are available to me leave the impression that, even when vitamin D is also ingested the utilization of calcium by children 11 to 15 years of age is more variable than at any other period with the possible exception of infancy Many such children given an excellent diet show little or no retention of calcium for several weeks after the establishment of the regimen[5] Johnston[35] observed that girls of this age group showed a sharp decrease in calcium retention at or near the menarche Calcium retention could be increased by increasing the amount of vitamin D ingested but was satisfactory only when 3 000 I U or more were ingested daily In our own laboratory similarly poor retention of calcium (from 10 to 150 mg daily) was observed in both boys and girls, 11 to 14 years old whose nutrition had been somewhat substandard for several years though the children were within normal range for both weight and height Alternate increases of milk and vitamin D permitted adequate retention only when 2 quarts (2 000 ml) of milk and 700 or 800 I U of vitamin D were ingested daily The children by this time had been under

34 (a) Macy I G Nutrition and Chemical Growth in Childhood II. Chemical Data Springfield Ill. Charles C Thomas, 1946. (b) Jeans P C and Stearns G Unpublished data

35 Johnston J A Factors Influencing the Retention of Nitrogen and Calcium in the Period of Growth IV Effect of Estrogens Am. J Dis Child. 62:703 1941

mineral requirements will drop to the adult or maintenance level Until more accurate knowledge is at hand it seems wiser to continue the high intake of bone minerals through late adolescence and early adult life

Pregnancy and Lactation —Pregnancy and lactation are periods of added stress for the young woman The effect of adverse nutrition on the developing embryo makes it especially important that the young woman maintain fully adequate nutrition before becoming pregnant Such nutrition would insure her own skeleton being fully mineralized when pregnancy occurs Little mineral is used by the fetus until the last trimester of pregnancy During this period approximately 25 Gm are deposited in the baby s body, or roughly 0 3 Gm daily during the last trimester must be stored over and above the mother s own need Fortunately, during this period the endocrine balance of the body appears to favor retention despite the marked increase in urine calcium which occurs in late pregnancy[38] Most women can maintain the needed retention with an intake of 1 5 Gm of calcium daily if vitamin D is also ingested If milk is the chief source of calcium and the diet contains ample amounts of fruits and vegetables the magnesium and phosphorus intake will be ample also

For some reason as yet not clear it appears to be more difficult for a lactating woman to maintain the calcium content of her body than for the pregnant woman to do so Urinary calcium is usually lower in the lactating than in the nonpregnant woman[39] The calcium excreted in urine plus that of the milk may be no greater than the urinary excretion of calcium during late pregnancy yet calcium will be lost from the body unless the intake is maintained at a higher level than during pregnancy[40] For this reason the National Research Council allowances have been placed at 2 0 Gm daily which seems a reasonable increase

Periods of lactation exceeding nine months appear to be accompanied with profound metabolic changes resulting in heavy calcium loss The only reported data on women lactating for a year or more[40] showed

39 Kn pp E L Stud es on Urinary Excret on of Calcium thesis St te Un ers ty of Iow 1943

40 Don lson E Nims B Hunscher H A and Macy, I G M tabol sm of Women During the Reproduct ve Cycle Calcium and Phosph rus Util t on in Late Lactat on and During Subsequent Reproduct ve Re t J B ol Chem **91** 675 1931

growth spurt occurs before the child reaches 13 years Thus, if adequate storage is provided for this rapid growth, it would seem wise to provide an increased intake of calcium and phosphorus earlier than National Research Council recommendations even by 8 to 10 years of age Such provision would permit filling of storage depots before the period of most rapid skeletal growth and insure, through ingestion of an ample diet, better utilization of minerals during the period of rapid growth

The ingestion of 1 quart of milk daily plus a diet otherwise adequate will provide 1 3 to 1 6 Gm of calcium Such quantities should provide ample amounts for the well nourished preadolescent and the adolescent child The boy or girl whose growth is unusually rapid could benefit, or would certainly suffer no harm from an additional amount of milk The ingestion of a moderate amount of vitamin D seems a necessary safeguard for this age group

It must be stressed that recovery from poor nutrition is not complete within a few weeks Particularly in the adolescent group, recovery from mineral under nutrition is slow and achievement of good absorption may occur only after many months of good dietary regimen Complete mineralization of the skeleton may take years after growth is completed In the report of the first White House Conference on Child Health and Protection, Todd[37] wrote of "the physiological osteoporosis of adolescence" Although osteoporosis was the common observation in this age group then, and probably is now, it is not known whether such depletion is unavoidable or represents inadequate nutrition preceding and during the period of rapid growth Sherman[38] has shown that such skeletal depletion can occur in rats during growth and that, in such animals achievement of a completely mineralized skeleton may be delayed until middle age, if the intake of mineral is maintained at a low level

Because of these observations it seems unsafe to consider that as soon as growth in height is complete

37 Venar Y A and Todd T W In White House Conference on Child Health and Protection II Anatomy and Physiology New York D Appleton Century Company 1932

38 Sherman H C Calcium and Phosphorus in Foods and Nutrition New York Columbia University Press 1947

than now, so that the requirement for each component of the diet has been studied with diets of widely varying compositions allowance must continue to be made for the apparently greater requirement of any one essential when the diet is inadequate in other essentials Thus the National Research Council allowance of 1 Gm daily for adults seems moderate Such an amount of calcium can be maintained by the ingestion of 1 pint of milk daily together with a serving of milk products as cheese or ice cream and cream used in coffee. Three glasses of milk daily provide an ample intake.

Ohlson and collaborators [42] have studied the calcium metabolism of women from 52 to 74 years old and found the mean requirement for equilibrium was 14 1 mg per kilogram of body weight considerably higher than Mitchell s mean findings for vigorous adults

It has been observed that gastric acidity tends to decrease *in old age so it is not surprising that the* absorption of calcium phosphorus and magnesium is not efficient in older persons Their requirements therefore resemble those of young children The diet should be adequate in all respects and the food easily assimilable A gram or more of calcium daily, taken largely from milk, seems highly desirable for the elderly adult. The ingestion of a moderate amount of vitamin D daily would appear as necessary for the sedentary elderly person as for the child for older persons may not be exposed to sunlight regularly

Osteoporosis is all too common in middle-aged and older women somewhat less common but not rare among older men Whether such osteoporosis is due primarily to atrophy of the bone matrix [43] to loss of mineral or to both is not yet fully established Albright [44] has shown that remineralization occurs *in osteoporosis* during therapy with steroid hormones which are known to stimulate anabolism The *remineralization was con-*comitant with increased retention of nitrogen calcium and phosphorus Remineralization in osteoporosis has also been observed after diet and other therapy directed toward improving absorption from the gastrointestinal

42 Roberts, P H , Kerr C. H and Ohlson M A. Nutritional Status of Older Women, J D etet. A. **24**:292 (April) 1948.

43 Albright F Smith, P H., and Richardson A. M. Postmenopausal Osteoporosis J A. M A **116**:2465 (May 31) 1941

44 Albright, F and Reifenstein E. C. The Parathyroid Glands and Metabolic Bone D sease Selected Studies, Baltimore, Williams & Wilkins Company 1948

that most of the subjects studied excreted excessive amounts of calcium in urine, amounts exceeding 1 Gm daily (for one subject) and accompanied with marked loss of this mineral from the body These women were professional donors to a human milk depot It appears that in assessing the value of such depots one must consider the ultimate cost to the women who provide milk by overly long lactation periods

Adults—After complete mineralization of the skeleton has been achieved, the adult man and the woman who does not bear children need only sufficient minerals for body maintenance

Studies of adults[41] show that healthy men and women receiving a diet adequate in all known essentials will be in calcium equilibrium (losses and retention remaining equal over a period of time) when the calcium intake is 10 mg per kilogram of body weight Thus were an adult always in perfect health an intake of 0 5 to 0 8 Gm of calcium daily should be adequate, depending on the weight of the person Steggerda and Mitchell[41b, c] reiterated that an intake of 10 mg per kilogram of body weight daily represented the mean adult requirement and that increasing the daily intake to 14 51 mg per kilogram of body weight (1 Gm daily for a 150 pound [68 Kg] man) would cover the requirements of 90 per cent of adult men and women of a nutritional status representative of college students and staff These values can be considered representative of a favored population group ingesting fully adequate diets They do not take into account the fact that adults also have illness and that worry and mental strain decrease gastrointestinal efficiency McKay and collaborators[41d] demonstrated that calcium and phosphorus retention of college women was greater for a given intake when a completely adequate diet was given than when the subjects chose their own food Until the practice of nutrition is far better established

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41 (*a*) Steggerda F R and Mitchell H H The Calcium Requirement of Adult Man and the Utilization of the Calcium in Milk and in Calcium Gluconate J Nutrition **17**: 253 1939 (*b*) Further Experiments on the Calcium Requirement of Adult Man and the Utilization of the Calcium in Milk ibid. **21** 577 (June) 1941 (*c*) Variability in the Calcium Metabolism and Calcium Requirements of Adult Human Subjects ibid **31** 407 (April) 1946 (*d*) McKay H Patton M B Ohlson M A Pittman M S Leverton R Marsh A G Stearns G and Cox G Calcium Phosphorus and Nitrogen Metabolism of Young College Women J Nutrition **24** 367 (Oct) 1942 McKay H Patton M B Pittman M S Stearns G and Edelblute N The Effect of Vitamin D on Calcium Retentions J Nutrition **26**: 153 (Aug) 1943

believed, it seems equally possible that loss of magnesium during periods of illness may be far greater than is realized, necessitating greater storage during periods of retention Duckworth and Godden[47b] have observed that, in animals depleted of magnesium, the magnesium of bone is used to maintain the magnesium content of the soft tissues Repletion of bone is a much slower process than depletion

Phosphorus—Phosphorus is so universal in American foods that an intake deficient in phosphorus must of necessity be deficient in a large number of food essentials In addition phosphorus appears to be more efficiently absorbed from the gastrointestinal tract than either calcium or magnesium

If the dietary requirement for calcium is met from milk the phosphorus intake will be adequate All protein rich foods are good sources of phosphorus During the periods of growth which include infancy, childhood pregnancy and lactation the amount of calcium in the diet should equal or exceed the amount of phosphorus with a ratio of calcium to phosphorus from 1 to 1 5[48] In periods of maintenance only, as in adult life the ratio may be less than 1

COMMENT

The supply of bone building minerals during periods of growth is an important factor in determining the eventual stature of a person Study of dietary habits of various groups tend to show that peoples whose diets provide adequate calories protein and calcium are tall in stature and those whose diets are poor in these substances tend not only to be short in stature but small framed with finer bone structure and a thinner bone cortex If children of such small skeletoned peoples are more liberally fed significant increase in stature is observed even in one generation It is not the province of this review to discuss the proper height or skeletal size of the American people, yet to speak of requirement of these substances for any age group presupposes a standard both for final stature and for rate of skeletal growth The discussion of requirements herein has been based primarily on growth rates of nutritionally favored population groups The term

48 Stearns G The Significance of the Retention Ratio of Calcium Phosphorus in Infants and in Children Am. J Dis Child 42:749 (Oct.) 1931

tract[45] For the purpose of this review the important fact appears to be that gastrointestinal efficiency of many elderly persons is poor and special therapy may be needed to improve absorption of food constituents

Magnesium —Little has been added to our knowledge of magnesium requirements since the publication of the excellent review by Duckworth and Warnock[21] Magnesium is widely distributed among foodstuffs, though the quantity present in any single food is not large The magnesium content of human milk averages 4 mg per 100 milliliters and that of cow's milk 12 mg per 100 milliliters[25e] roughly one-eighth and one tenth the calcium content of the two kinds of milk Meats and cereals contain more magnesium than calcium, vegetables and fruits show variable proportions of the two components

The effects of magnesium deprivation have been *rather fully studied in animals*[46] *However, mag*nesium is so widely distributed in foodstuffs that magnesium deficiency, if it occurs in man is probably the result of lack of utilization rather than of deficient intake[28]

Duckworth and Warnock have estimated the magnesium requirement as less than 10 mg daily during growth If these estimates are correct and they are based on sound premises, it would seem difficult to avoid an adequate intake of magnesium Recorded magnesium intakes of various groups of infants and *children*[47] *showed mean values varying* from 100 mg to 300 mg daily corresponding mean retention values varied from 10 to 78 mg daily, with a median of about 21 mg As was pointed out by these reviewers the apparent retention of magnesium by children at all ages studied is much more than the amount estimated as needed Duckworth and Warnock concluded that excretion in sweat must be far greater than is generally

45 Meulengracht E Osteomalacia of the Spinal Column from Deficient Diet or from Disease of the Digestive Tract I From Deficient Diet, Acta med Scandinav **101** 138 1939 II Osteomalacia Achylia ibid **101:** 157 1939 III Osteomalacia e Abuse Laxantium ibid. **101:** 187 1939 Stearns G and others Unpublished data

46 Kruse *H D* Orent *E R* and McCollum *E V* Studies on Magnesium Deficiency in Animals I Symptomatology Resulting from Magnesium Deprivation, J Biol Chem **96:** 519 1932 Greenberg[84]

47 Shukers C F Knott E M and Schlutz F W Magnesium Balance Studies with Infants J Nutrition **22** 53 (July) 1941 Daniels, A. L and Everson G J A Study of the Magnesium Needs of Preschool Children J Nutrition **11** 327 (April) 1936 Daniels A L Magnesium Needs of Preschool Children Am J Dis Child **62:** 568 1941

CHAPTER V

IRON AND COPPER

WILLIAM J DARBY

Several recent well documented reviews of iron metabolism are available for those who may be interested in detailed discussions of the subject Especially to be recommended to the physician are the classical review of Heath and Patek[1] and the discussions by Moore[2] and by Cartwright[3] Accordingly this paper will deal specifically with some aspects of iron metabolism which relate directly to an understanding of the clinical syndrome of iron deficiency as encountered in man and its prevention and treatment This paper is intended to supplement, not to supersede the excellent discussion of iron in nutrition contained in the first edition of the 'Handbook of Nutrition'[4]

The importance of iron deficiency may be illustrated by noting that in the Vanderbilt University Hospital clinics it is the most frequently encountered clinically manifest deficiency disease It is most often seen in women during the childbearing period and the menopause and in children from 6 months to 2 years of age The explanation of this distribution will be apparent in the discussion which follows When encountered in adults the disease is rarely if ever, of dietary origin and must be regarded as evidence of abnormal blood loss

METABOLISM OF IRON

The earlier knowledge of iron metabolism was based on studies which employed the usual metabolic balance

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1 Heath C W and Patek A J Jr The Anemia of Iron Deficiency Medicine 16: 267 (Sept.) 1937

2 Moore C V Iron Metabolism and Hypochromic Anemia Symposia on Nutrition I Nutritional Anemia Cincinnati The Robert Gould Research Foundation Inc 1947 p 117

3 Cartwright G E Dietary Factors Concerned in Erythropoiesis Blood 2: 111 (March) 256 (May) 1947

4 Heath C W Iron in Nutrition Handbook of Nutrition, Chicago American Medical Association, 1943 p 115

allowance as used by the National Research Council is probably preferable to the term requirement Certainly, a considerable part of our own population has lived to maturity reared children and died without ever achieving such a daily intake as recommended here. It is equally certain that a considerable percentage of our population shows some degree of malnutrition as judged by present standards The prevalence of osteoporosis in older persons is often considered evidence of such malnutrition Whether better dietary habits, including a more ample intake of bone building minerals, will result in a more vigorous old age remains to be proved The evidence is strong that better nutrition is one of the chief factors in the increase of stature and of rate of growth of present day Americans over those of fifty years ago As the mean age of our population increases we are concerned with postponement of senescence Maintenance of a well mineralized skeleton throughout adult life may well be a factor in the maintenance of physical vigor into old age Studies of skeletal density and the prevalence of bone diseases in older populations in which dietary habits can be ascertained throughout their adult years would add materially to our knowledge of these matters

Our present knowledge of the requirements for skeletal minerals can be summarized simply Ample evidence exists that deficiency of intake or utilization of these minerals results in slowing of growth and lengthening of the growth period it is possible that such deficiencies in adult life may hasten senescence On the other hand there is no evidence of any ill effects from ample intake of these substances over long periods of time, during the growth period increased ingestion of milk with its high content of bone minerals has been accompanied with increase in rate of growth and earlier completion of growth The evidence favors strongly the maintenance of an adequate even ample, intake of these minerals throughout the entire life span

α α-dipyridyl Iron so determined in foodstuffs has often been termed 'available iron' There is evidence that some correlation may exist between iron which reacts in this manner and the availability of such iron to rats for hemoglobin synthesis [7] but similar studies of the relationship in man are lacking Availability studies of iron compounds carried out on other species, such as rats or dogs, should not serve as more than a tentative basis for conclusions regarding the availability or absorbability of iron by man This statement is based on the findings of Moore and his co-workers [8] and Hahn and his collaborators,[9] both of whom employed radioactive iron in a study of the relative absorbability by man of ferrous and ferric iron Both groups of investigators found that ferrous iron was absorbed much more readily by man than was ferric iron These results were in distinct contrast to similar studies in the dog which proved that ferric iron is absorbed by this species equally as well as ferrous iron Obviously therefore, conclusions based on observations on lower animals are not necessarily valid for man Investigations of the absorbability or availability of iron products must be verified by studies in man before they serve as a basis for decisions on policies concerning enrichment of foodstuffs with iron The evidence indicates that iron absorption in the rat and dog is similar This evidence demonstrates the fallacy inherent in the interpretation of existing evidence for the availability of several iron-containing products which may be used in bread enrichment [10] The use of the dog [11] as an experimental animal

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7 Chatfield, C and Adams, G Food Composition in "Food and Life, Yearbook of Agriculture Washington D C United States Department of Agriculture 1939 p 272

8 Moore C V Dubach R Minnich V and Roberts H K Absorption of Ferrous and Ferric Radioactive Iron by Human Subjects and by Dogs J Clin Investigation 23:755 (Sept) 1944

9 Hahn P F Jones E Lowe R C Meneely G R and Peacock, W The Relative Absorption and Utilization of Ferrous and Ferric Iron in Anemia as Determined with the Radioactive Isotope Am J Physiol. 143 191 (Feb) 1945

10 Freeman S and Burrill M W Comparative Effectiveness of Various Iron Compounds in Promoting Iron Retention and Hemoglobin Regeneration by Anemic Rats J Nutrition 30:293 (Oct) 1945 Blumberg H and Arnold, A The Comparative Biological Availabilities of Ferrous Sulfate Iron and Ferric Orthophosphate Iron in Enriched Bread ibid 34 373 (Oct) 1947

11 Fuegamer W R Michaud L Hart E B and Elvehjem C A The Use of the Dog for Studies on Iron Availability J Nutrition 32 101 (July) 1946

technic The past decade has seen the development and widespread application of investigations using radio active or labeled iron The principle of this latter type of investigation is simple the investigator administers the desired quantity (usually quite small and within the physiologic range) of iron, which is tagged by the presence in the sample of varying amounts of one of the radioactive isotopes of iron[5] Subsequently at intervals blood, excreta or tissues are sampled and ashed and determinations are made of the radioactivity of the iron contained in these substances[6] One may thereby deter mine the location of atoms of iron which were admin istered at the determined time Up to the instant of decay radioactive isotopes are physiologically indis tinguishable from the ordinary nonradioactive variety Hence, one may assume that the fate of the radioactive atom is indicative of the fate of all the atoms of iron in the administered sample Accordingly a judicious use of quantitative determinations of total iron and radio activity in such studies permits one to obtain valuable knowledge of the course of iron in metabolism

Iron exists in foodstuffs in a variety of forms certain of which are but slightly absorbed In some instances the poor absorbability of iron is due to the presence of the metal in a sparingly soluble compound or in an organic form from which the iron is poorly liberated In other instances the differences in the absorbability of iron at least in pharmaceutic preparations, are based on differences in valence states of the metal

It has been held that the availability of iron from a foodstuff could be ascertained by a determination of the amount of iron in the substance which reacted with

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5 Two radioactive isotopes of iron have been employed Fe with a half life of forty-seven days, and Fe^{55} with a half life of five years (For a discussion of these technics see footnotes 6 and 8 and Hevesey G Radioactive Indicators Their Application in Biochemistry Animal Physiology and Pathology Interscience Publishers Inc New York 1948 p 556)

6 (a) Hahn P Radioactive Iron Procedures Indust & Engin Chem **17**: 45 (Jan) 1945 Balfour W M Hahn P F Bale W F Pommerenke W T and Whipple G H Radioactive Iron Absorption in Clinical Conditions Normal Pregnancy Anemia and Hemochromatosis J Exper Med. **76**: 15 (July) 1942 (b) Dubach R Moore C V and Minnich V Studies in Iron Transportation and Metabolism J Lab & Clin Med. **31**: 1201 (Nov) 1946

reduces ferric iron and there is evidence that it may serve this role under physiologic conditions

The control of iron absorption by the intestinal mucosa may be mediated through the iron-containing protein ferritin This protein may incorporate up to 23 per cent of iron which it may readily release The iron free protein is called "apoferritin" Ferritin is known to serve as a repository for iron in the body, and Granick[18] has pictured its role in iron absorption as illustrated by figure 1 This does not appear to be a final picture of the actual mechanism of iron absorption but serves to emphasize the controlled nature of the process and a probable role of ferritin in it

Absorbed iron is transported in the plasma in the ferric state as one of the globulin fractions[19] The quantitative determination of serum iron is of such value that it warrants more widespread use in this country A

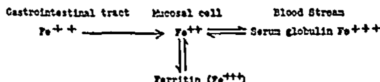


Fig 1—Granick's scheme[18] indicating a role of ferritin in absorption of iron.

recently described microprocedure[20] should extend the range of usefulness of the measure The normal range of values for serum iron is usually stated to be 80 to 180 micrograms per hundred milliliters Low values are encountered in the hypochromic microcytic anemia of iron deficiency and in the anemia of infection Higher than normal values are met in pernicious anemia and possibly in the other macrocytic anemias although the evidence on some of these latter is insufficient to permit a categorical statement

Iron which is given intravenously disappears from the plasma until a level of between 300 and 400 micrograms per hundred milliliters is established The measure of the concentration of iron which can

18 Granick S Ferritin IX Increase of the Protein Apoferritin in the Gastrointestinal Mucosa as a Direct Response to Iron Feeding The Function of Ferritin in the Regulation of Iron Absorption J Biol. Chem. **164:** 737 (Aug) 1946

19 Schade A L and Caroline L An Iron Binding Component in Human Blood Plasma Science **104:** 340 (Oct 11) 1946

20 Burch H B Lowry O H Bessey O A and Berson B Z The Determination of Iron in Small Volumes of Blood Serum J Biol. Chem **174** 791 (July) 1948

for studies on iron availability obviously does not circumvent this fallacy if the data are to be applied to man

Simultaneously ingested food may decrease iron absorption in man,[12] an effect which may be attributable in part to the effect of bulk[12] It is reported that certain types of diets may increase the absorption of iron[13] in the rat—an effect which calls to mind the occurrence of ferremia and hemosiderosis in pyridoxine-deficient animals[14]

The absorption of iron from the gastrointestinal tract is normally a controlled process[15] In the healthy, non deficient adult only a small portion of ingested food iron will be absorbed each day In an iron-deficient person the absorptive process is much more efficient, and a high percentage of the ingested iron may be taken up Studies of iron absorption in growing children indicate that the efficiency of the absorption process parallels the need for the element[16] Similarly during the latter half of pregnancy the absorptive efficiency is greatly increased[17] this being the period during which the fetal iron stores are built up

As indicated, ferrous iron is more efficiently absorbed than ferric iron The implication of this observation in therapy is obvious It seems probable that all iron which is absorbed must first be reduced to the ferrous state[17a] Accordingly, the presence of conditions in the gastrointestinal tract conducive to reducing iron to this state is of importance. Ascorbic acid

12 Sharpe L. M Harris R S Peacock, W C and Cooke R. C Effect of Phytate and Other Food Ingredients on the Absorption of Radioactive Iron, Federation Proc. 7 298 (March) 1948 Harris R. S Personal communication to the author

13 Hegsted D M Finch, C A and Kinney T D The Effect of Diet upon Iron Absorption, Federation Proc 7:290 (March) 1948

14 Cartwright, G E Wintrobe M M and Humphreys S Studies on Anemia in Swine Due to Pyridoxine Deficiency Together with Data on Phenylhydrazine Anemia J Biol. Chem. **153**:171 (April) 1944

15 McCance R. A and Widdowson, E. M Absorption and Excretion of Iron, Lancet 2 680 (Sept 18) 1937 Hahn P F Bale W F Hettig R A Kamen M. D and Whipple G H Radioactive Iron and Its Excretion in Urine Bile and Feces J Exper Med. **70** 443 (Nov) 1939 Footnote no 4

16 Darby W J Hahn, P F Kaser M M Steinkamp R C. Densen P M and Cook, M B The Absorption of Radioactive Iron by Children Seven to Ten Years of Age J Nutrition **33** 107 (Jan.) 1947

17 Hahn P F Carothers, E L Cannon R. O Sheppard, C. W Darby W J Kaser M M McClellan, G S and Densen P M Iron Uptake in Seven Hundred and Fifty Cases of Human Pregnancy Using the Radioactive Isotope Fe^{59} Federation Proc. 6 392 (March) 1947

17a Kirch E R. Bergeim O Kleinberg J and James S Reduction of Iron by Foods in Artificial Gastric Digestion, J Biol. Chem. **171**: 687 (Dec) 1947

are summarized in tables 1 and 2 indicate that the times of the greatest requirement for iron, both relatively and absolutely, are during the first two years of life and the rapid growth of adolescence and in women, throughout the childbearing period After growth ceases in the man the requirement for iron falls to an exceedingly low level For women the requirement remains higher because of the loss of iron in menstrual blood and the process of reproduction After the menopause the requirement drops These requirements were cal-

TABLE 1—*Iron Requirements for Growth (Males)**

Year of Life	Total Annual Requirement of Iron (Gm)
1..	0 10
2..	0 11
3	0 060
4	0 0[illegible]
5..	0 098
6.	0 079
7..	0 090
8	0 070
9..	0 07[illegible]
10	0 15
11	0 130
12	0 137
13..	0 180
14	0 198
15..	0.314
16	0 313
17	0 3[illegible]3
18..	0 183
19..	0 149
20	0 081
21	0 071
22..	0
23..	0
Total requirement birth to 21 years	3 148

* From Heath and Patek [1]

culated from estimates of the iron needed to build body tissue and to replace body losses They are not estimates of dietary requirements The Food and Nutrition Board of the National Research Council has given estimates of allowances of iron in the diet in order to provide an abundantly adequate supply of dietary iron The figures from the 1948 revision are reproduced in table 3 Somewhere between these two estimates probably lies the true minimal dietary requirement of the metal

I feel that it will remain futile to attempt to set a single figure as the requirement for iron in the diet

be retained by the plasma under such circumstances is spoken of as the iron binding capacity of the serum Cartwright[21] has shown that the hypoferremia of chronic infections is accompanied by a decrease in the iron binding capacity of the serum and that this latter may be increased by administration of a globulin fraction

Iron is stored in the tissues, most likely in a number of compounds The storage iron appears to exist in two parts (1) a readily available "labile iron pool,'[22] which is made up of recently absorbed iron plus that recently released during the breakdown of hemoglobin, and (2) a more fixed, less readily available, tissue iron The chief sites of storage iron are liver spleen bone marrow and kidneys

In addition to storage iron the tissues contain so called parenchymal iron" which is the relatively fixed iron present in muscle and other tissues and not contained in muscle hemoglobin Parenchymal iron is held in the iron containing enzymes such as cytochrome catalase peroxidase and related compounds Parenchymal iron and muscle hemoglobin have been termed by Hahn[23] as "inviolate stores of iron which are not drawn on no matter how great the emergency due to anemia'

The body has a minimal capacity for losing iron except through blood loss[15] Practically no iron is excreted in the urine and the excretory iron in the feces comprises less than 1 0 mg per day[24] Moore[25] has failed to confirm the claim of Mitchell and Hamilton[26] that a large loss of iron occurs through the perspiration

REQUIREMENTS FOR IRON

The calculations of iron requirements which were made by Heath and Patek[1] are probably as valid as any which could be made today These estimates which

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21 Cartwright G E. Studies on the Iron Binding Capacity of Serum Symposia on Nutrition I Nutritional Anemia Cincinnati The Robert Gould Research Foundation Inc 1947 p 116

22 Greenberg G I and Wintrobe M M A Labile Iron Pool J Biol Chem **165** 397 (Sept) 1946

23 Hahn P F The Metabolism of Iron Medicine **16** 249 (Sept.) 1937

24 Moore C V Estimated from data of Dubach Moore and Minnich b on Excretion of Intravenously Injected Iron in Patients with Hemolytic Anemia

25 Moore C V Iron Metabolism and Hypochromic Anemia, paper presented at Symposium Currents in Nutrition University of Illinois College of Medicine Chicago November 19 1949

26 Mitchell H H and Hamilton T S The Dermal Excretion under Controlled Environmental Conditions of Nitrogen and Minerals in Human Subjects with Particular Reference to Calcium and Iron J Biol. Chem **178**: 345 (March) 1949

are summarized in tables 1 and 2 indicate that the times of the greatest requirement for iron, both relatively and absolutely, are during the first two years of life and the rapid growth of adolescence and in women, throughout the childbearing period After growth ceases in the man, the requirement for iron falls to an exceedingly low level For women the requirement remains higher because of the loss of iron in menstrual blood and the process of reproduction After the menopause the requirement drops These requirements were calculated from estimates of the iron needed to build body tissue and to replace body losses They are not estimates of dietary requirements The Food and Nutrition Board of the National Research Council has given estimates of allowances of iron in the diet in order to provide an abundantly adequate supply of dietary iron The figures from the 1948 revision are reproduced in table 3 Somewhere between these two estimates probably lies the true minimal dietary requirement of the metal

TABLE 1—*Iron Requirements for Growth (Males)**

Year of Life	Total Annual Requirement of Iron (Gm)
1	0.195
2	0.112
3	0.060
4	0.07
5	0.098
6	0.079
7	0.090
8	0.070
9	0.072
10	0.15
11	0.130
12	0.137
13	0.180
14	0.198
15	0.314
16	0.313
17	0.353
18	0.193
19	0.149
20	0.061
21	0.071
22	0
23	0
Total requirement birth to 21 years	3.148

* From Heath and Patek [1]

I feel that it will remain futile to attempt to set a single figure as the requirement for iron in the diet

The physiologic availability of iron varies from food stuff to foodstuff and is dependent on the composition of the remainder of the diet For all nutrients there exist important physiologic variations in requirements from person to person Accordingly, any single figure for requirements must remain a mere approximation

At this point, it may be well to consider terminology concerning physiologic availability of iron It has been pointed out that the term "available iron has been used

TABLE 2—*Iron Requirements for Growth Menstruation and Pregnancy* *

Year of Life	Total Annual Requirement of Iron (Gm)
1	0 183
2	0 11
3	0 09[illegible]
4	0 080
5	0 087
6	0 106
7	0 0[illegible]3
8	0 067
9	0 108
10	0 1[illegible]0
11	0 163
12	0 164
13	0 19[illegible]
14	0 145
15	0 468
16	0 4[illegible]4
17	0 498
18	0 435
19	0 45
20	0 [illegible]65
21	0 358
2[illegible]	0 [illegible]98
[illegible]3	0 298
24	0 298
[illegible]5	0 3[illegible]4 †
26	0 [illegible]98
Total requirement birth to 47 years	12 2[illegible]2

* From Heath and Patek
† Calculated for pregnancy

in connection with a chemical procedure which does not necessarily measure the iron which can be absorbed and utilized by man It appears to be mandatory that *iron is in the ferrous state at the moment of absorption* by man Therefore all the iron which is absorbed from the human intestine would seem to enter the body with the same potentialities for utilization regardless of the original form of the iron Accordingly it appears to me that the use of the term absorbable iron in foodstuffs would be a more precise and useful term than 'utilizable or available iron

The total iron content, expressed in milligrams per hundred grams, of the edible portion of some representative foods are listed in table 4 The values given in this table permit the following generalizations Relatively rich sources of iron are organ meats (heart and liver), egg yolk dried legumes, oatmeal and cane molasses Poor sources of iron include milk and milk products, fats and oils, fruits and root vegetables, unenriched white flour, granulated sugar and degerminated

TABLE 3—*Recommended Daily Dietary Allowances*

	Iron (Mg)
Man (154 lb 70 kg)	
Sedentary	12
Physically active	12
With heavy work	12
Woman (123 lb 56 kg)	
Sedentary	12
Moderately active	12
Very active	12
Pregnancy (latter half)	15
Lactation	15
Children up to 12 years	
Under 1	6
1-3 (27 lb 12 Kg)	7
4-6 (42 lb 19 kg)	8
7-9 (58 lb., 26 kg)	10
10-12 (78 lb 35 Kg)	12
Children over 12 years	
Girls 13-15 (108 lb 49 Kg)	15
16-20 (122 lb 55 Kg)	15
Boys 13-15 (108 lb 49 kg)	15
16-20 (141 lb 64 kg)	15

There is evidence that the male adult needs relatively little iron. The need will usually be provided for if the diet is satisfactory in other respects

cornmeal Foods of intermediate iron content include muscle meats fish poultry nuts green and green leafy vegetables enriched flour and whole grain meal

IRON DEFICIENCY

The pathogenesis of iron deficiency is usually predictable from the age of the person In the infant iron deficiency is most often of dietary origin In the adult the deficiency is conditioned by chronic blood loss

The fetal stores of iron are deposited during the last trimester of pregnancy Although the interpretation has been questioned there is considerable evidence to

TABLE 4—*Iron Content of Selected Foods**

Food Item	Iron (Mg / 100 Gm) †
Milk	
Evaporated unsweetened	17
Fresh whole	.07
Ice cream plain	10
Cheese Cheddar type	57
Bacon medium fat	.8
Butter	.2
Lard other shortening	0
Egg yolk fresh	7.2
Eggs whole fresh	2.7
Beef	
Roasting meat	2.8
Round steak (wholesale round)	2.9
Pork Ham smoked	2.5
Variety meats meat mixtures	
Heart fresh	6.2
Liver fresh	12.1
Poultry chicken roasters	1.9
Fish miscellaneous medium fat	1.0
Dry Beans and Peas Nuts	
Cowpeas	7.8
Peanuts roasted	1.9
Vegetables Fresh	
Beans lima green	2.3
Beets	1.0
Broccoli	1.3
Carrots	.8
Kale	2.2
Lettuce headed	.5
Mustard greens	2.9
Potatoes	7
Spinach	3.0
Turnip greens	2.4
Turnips	5
Fruit Fresh	
Apples	.3
Apricots	.5
Cantaloupes	4
Grapefruit	.3
Oranges	.4
Corn meal	
White degerminated	1.0
White whole grain	2.7
Flour	
Wheat patent	7
Wheat patent enriched	2.0
Whole wheat	3.8
Bread	
White enriched	1.8
Whole wheat	2.0
Cereals	
Oatmeal	5.2
Rice flakes puffed rice	.9
Sugars Sweets	
Honey	9
Molasses cane	6.7
Sugar brown	2.6
Sugar granulated or powdered	1
Yeast dried brewer's	18.2

* From the United States Department of Agriculture Miscellaneous Publication No 572 † Edible portion

indicate that fetal stores of iron at birth may be considerably influenced by the nutrition of the mother relative to iron during pregnancy Thus Strauss[8] found that infants born to mothers who were anemic during pregnancy had a high incidence of iron deficiency anemia during the first year of life The iron stores of premature infants are less than those of full term infant At birth a considerable amount of iron is contained in the infant's body because of the plethora of red cells and hemoglobin Normally the iron available from the breakdown of the excessive hemoglobin and from normal stores will be sufficient to carry the infant through the first few months of life on the low iron intake provided by milk From approximately 6 months of age on however the body stores of iron may be insufficient to meet the demands of the growing infant and unless an intake of iron other than that contained in milk is provided the hypochromic microcytic anemia of iron deficiency may appear This manifestation of iron deficiency is most frequently encountered in children from 6 months to 2½ years of age who have received a diet based on cow's milk formula From table 4 it is apparent that the provision of orange juice as an antiscorbutic and vitamins A and D in a fish oil would not suffice to protect the infant against the development of iron deficiency This illustrates the desirability of a variety of foods in the infant's diet

The clinical evidence indicates that by the time adulthood is reached even the poorest dietary regimens which are likely to be encountered in this country are sufficient to prevent iron deficiency in the absence of chronic blood loss Iron deficiency does not often occur as a result of a single massive hemorrhage Instead it results from repeated losses of blood The most common sources of these losses are menorrhagia functional or due to fibroids bleeding peptic ulcers hemorrhoids menopausal menorrhagia abortion miscarriage or bleeding after delivery parasitic infestation especially with hookworm and blood loss secondary to malignant changes either of the gastrointestinal tract nasopharynx or genitourinary tract Less frequently one finds that the fault lies in chronic pulmonary hemorrhage renal

7 Cue t C M Hypcf An n in Infa S mp s a on Nutri t n I Nit ti l Ann a C n nat Th R be t Could Re rch Fo nd t on In 194 p 144

8 St a M P An n f Int y f om M t nal Iron Deficiency n Pr gn ncy J Cl n I t g t n 12 345 (M h) 1933

hemorrhage (tuberculosis or hypernephroma) and blood losses from ulcerative colitis, rectal polyps or even diaphragmatic hernia.

Peculiarly enough, the pathology of iron deficiency has not been described in detail.[29] The iron deficient



Fig. —Glossitis, angular stomatitis and koilonychia encountered in patient with hypochromic microcytic anemia due to menorrhagia. These lesions as well as the anemia responded to therapy with ferrous sulfate alone.

person usually is rather nervous, easily fatigued and listless; palpitation on exertion, a sore tongue, angular stomatitis and dysphagia may be present. A

29 Follis, R. H., Jr.: The Pathology of Nutritional Disease. Springfield, Ill.: Charles C Thomas, Publisher, 1948.

hypochromic microcytic anemia is invariably seen When all these conditions are present the syndrome is referred to as the Plummer-Vinson syndrome Koilonychia may also be seen Any combination of these conditions may be encountered [30] Signs other than the anemia are not usually encountered in children The oral lesions and nail changes are illustrated in figure 2 The oral lesions occur in one degree or another in about 10 per cent of iron-deficient adults, in my experience Koilonychia is less frequently met

The anemia of iron deficiency is hypochromic microcytic anemia and is accompanied by normoblastic hyper-

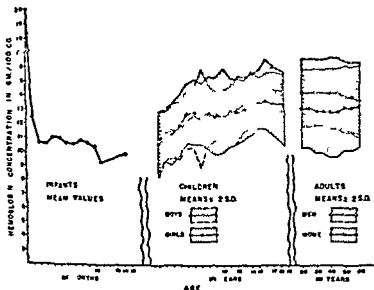


Fig 3—The variations in average hemoglobin concentrations throughout the life span are shown. This chart of mean hemoglobin concentration in grams per hundred cubic centimeters at various ages was constructed by accepting the value of 13 8 Gm per hundred cubic centimeters as 100 per cent (*Haldane*) The limits of plus or minus 2 standard deviations are such that one may expect them to include approximately 95 per cent of the values encountered in healthy persons Of particular interest are (1) the wide swings in hemoglobin level which occur between birth and adulthood, (2) the separation of means for boys and girls at puberty with the subsequent decrease in the sex differences after 40 years of age and (3) the greater variation in values for women than for men—a phenomenon more apparent at the menopause (Constructed from data of the Medical Research Council, Special Report Series no. 252 [31])

plasia of the bone marrow Plasma iron levels are low in this type of anemia Following the oral administration of ferrous sulfate some workers have reported

30 Heath and Patek [1] Darby W J *The Oral Manifestations of Iron Deficiency* J A M A. 130:830 (March 30) 1946 Waldenstrom J Iron and Epithelium Some Clinical Observations, Acta med. Scandinav 1938 supp 90 p 380

low or flat iron absorption curves[30a] while others have found that normal or somewhat elevated increases in serum iron occur[30b] At any rate iron absorption is increased as can be demonstrated by the use of radioactive iron technic

A discussion of anemia such as this raises the question of when a person or a population should be considered anemic The usual arbitrary figures for "normal hemoglobin and red blood cell values give no indication of the variability to be expected in a healthy population Several modern studies of hemoglobin levels in population groups other than hospital groups indicate something of this variability Figure 3 for example

TABLE 5 — *Distribution Constants of Hemoglobin Levels for White and Negro Populations (North Carolina)*[32]

	White Hemoglobin (Gm /100 Cc.)	Negro Hemoglobin (Gm /100 Cc)
Mean		
Under 12		
Boys	12 67 ± 0 046	11.89 ± 0 078
Girls	12.54 ± 0 046	12 13 ± 0 06
12 and over		
Men	14 25 ± 0 049	13.76 ± 0 086
Women	12 87 ± 0 043	12 16 ± 0 087
Women (fitted curve)	13 08	12 64
Limits of nineteen twentieths of distribution		
Under 12		
Boys	10 97 — 14 37	9 77 — 14.01
Girls	10 96 — 14 17	10 47 — 13 79
12 and over		
Men	11.88 — 16 69	11 31 — 16 21
Women	10 41 — 15 33	9.36 — 14 96
Women (fitted curve)	11.30 — 14.88	11 04 — 14.[illegible]

illustrates the variation in average hemoglobin levels which were encountered in different physiologic groups within populations in Great Britain[31] Table 5 indicates the variability in hemoglobin levels observed in a study of 3,029 persons in North Carolina[32] Like variations have been observed in other similar studies It is to be

30a Cartwright G E Lauritsen M A Jones P J Merrill I M and Wintrobe M M The Anemia of Infection I Hypoferremia, Hypercupremia and Alterations in Porphyrin Metabolism in Patients J Clin Investigation *XXV* 65 (Jan) 1946

30b Moore C V Arrowsmith W R. Welch Jo, and Minnich Virginia Studies in Iron Transportation and Metabolism IV Observations on the Absorption of Iron from the Gastro intestinal Tract, J Clin Investigation *XVIII* 553 (Sept.) 1939

31 *Haemoglobin Levels in Great Britain in 1943 (with Observations upon Serum Protein Levels)* Committee on Haemoglobin Surveys, Medical Research Council, Special Report Series no 252 London H s Majesty s Stationery Office 1945

32 Milam D F and Muench, H Hemoglobin Levels in Specific Race Age and Sex Groups of a Normal North Carolina Population J Lab & Clin Med 31:878 (Aug) 1946

noted that the lower limits of the nineteen twentieths of the distributions in the North Carolina studies are approximately 11 Gm for children under 12 years of age approximately 11.5 Gm for white women and approximately 12 Gm for white men In each case the values for the Negro groups are from 0.2 to 0.5 Gm less These lower limits represent a useful statistical division for those values likely to be associated with abnormality It is recognized that such average hemoglobin values do not necessarily indicate the level conducive to the best health Nevertheless such observations among a non ill population do caution against the designation of a large group of the population as anemic or iron-deficient[33] merely because they fall below some arbitrary hemoglobin levels especially in view of the clinical evidence that many of these persons cannot have their hemoglobin levels increased by the administration of iron[34]

The finding of a low hemoglobin level is not alone sufficient for the diagnosis of iron deficiency anemia whether in a particular person or a population group Unfortunately estimates of the prevalence of iron deficiency have sometimes been based on this single criterion[33] The simultaneous determination of hemoglobin concentration red blood cell counts (RBC) and of packed cell volume (PCV) permits the calculation of exceedingly useful volume and concentration indexes These indexes are as follows

$$\text{Mean corpuscular volume (MCV) in cubic microns} = \frac{\text{Volume of packed red cells (PCV) cc. per 100 cc.} \times 10}{\text{Red cell count (RBC) million per cu mm.}}$$

$$\text{Mean corpuscular hemoglobin (MCH) in micromicrograms} = \frac{\text{Hemoglobin Gm per 100 cc} \times 10}{\text{Red cell count (RBC) million per cu mm.}}$$

$$\text{Mean corpuscular hemoglobin concentration (MCHC) in per cent} = \frac{\text{Hemoglobin, Gm per 100 cc.} \times 100}{\text{Volume packed red cells (PCV) cc. per 100 cc.}}$$

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33 Committee on Diagnosis and Pathology of Nutritional Deficiencies, Food and Nutrition Board Inadequate Diets and Nutritional Deficiencies in the United States Their Prevalence and Significance New York, Bulletin of the National Research Council, no 109 1943

34 Fowler W M and Barer A P Some Effects of Iron on Hemoglobin Formation Am. J M Sc 201 642 (May) 1941

Table 6—*Classification of Principal Anemias (Modified after Wintrobe[85])*

Anemias	MCV (Cu µ)	MCHC (%)		Syndrome	Characterized by	Responds to
Hypochromic microcytic	< 80	< 30	A	Iron deficiency anemias of all sorts—including dietary deficiency excessive blood loss hookworm infestation and repeated pregnancies	Low serum iron normoblastic marrow	*Iron and correction* of blood loss
Simple microcytic	< 80	> 30		Subacute and chronic inflammatory diseases	Low serum iron hypercupremia	Treatment of cause
Normocytic	80 94	> 30	A	Myelophthisic and aplastic *anemias chronic disease*		Transfusion and treatment of cause
			B	Physiologic anemia (hydremia) of pregnancy		
Macrocytic	> 94	> 30	A	Pernicious anemia; Sprue; Pernicious anemia of pregnancy; Macrocytic anemia of celiac *disease*; Nutritional macrocytic anemia; Tropical macrocytic anemia; Macrocytic anemia associated with conditions such as carcinoma of stomach and liver disease	Megaloblastic marrow high or normal serum iron	*Liver extract folic* acid vitamin B_{12} or animal protein factor
			B	Conditions usually associated with normocytic anemias		Transfusions and *treatment of causes*

The usefulness of these indexes in the classification of anemias is indicated by table 6 which has been adopted from the report by Wintrobe[35]

In addition to these specific characteristics of iron deficiency anemia one may encounter the several manifestations of the anemic state In particular, one may observe cardiac abnormalities[36] such as hemic murmurs, cardiac enlargement symptoms of angina pectoris palpitation and even electrocardiographic changes Dyspnea and edema are not infrequently observed

The anemia of iron deficiency is most likely to be confused with anemias of infection hemolytic anemias and occasionally, myelophthisic anemias In animals, there are other types of microcytic anemia such as that due to pyridoxine deficiency or to cobalt deficiency The analogues of these however have not been identified in man

PREVENTION AND THERAPY OF IRON DEFICIENCY

The prevention of iron deficiency anemias in infants consists of proper attention to the nutritional state of the mother during pregnancy and the early introduction of a variety of foodstuffs in the diet of the baby It might be noted that breast milk is slightly richer in iron than cow s milk and accordingly breast feeding of the infant may be of aid in the prevention of the development of iron deficiency Once iron deficiency has developed therapy with a suitable preparation of a ferrous salt plus correction of the diet should result in a rapid recovery

The prevention of iron deficiency in the adult resides in the early recognition and correction of sources of chronic blood loss and in addition that which may be called 'preventive therapy or supplementation for those persons with conditions previously enumerated which impose the stress of excessive loss of iron in blood or during the latter part of pregnancy It is logical to reason that increasing the dietary intake of iron above the present level can be expected to have little influence on the prevalence of iron deficiency within the adult population

35 Wintrobe M M Anemia Classification and Treatment on the Basis of Differences in the Average Volume and Hemoglobin Content of the Red Corpuscles Arch Int Med 54 256 (Aug) 1934

36 (a) Hunter A The Heart in Anaemia, Quart. J Med. 15:107 (April) 1946 (b) Wintrobe M M The Cardiovascular System in Anemia, Blood 1 121 (March) 1946

The treatment of iron deficiency in the adult consists of detection of the source of blood loss and correction of the defect and the oral administration of a readily absorbed preparation of iron preferably ferrous sulfate The simple preparations of ferrous sulfate are equally as effective as any *combination of iron with yeast liver,* folic acid or other minerals Iron is effective only in the treatment of iron deficiency anemia It has no value in the treatment of the anemia of infection of pernicious anemia, sprue or other types of anemia unless they are accompanied by an associated iron deficiency Specific

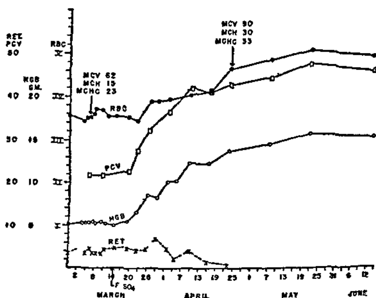


Fig 4 —Response of a patient with iron deficiency (microcytic hypochromic anemia) to ferrous sulfate administered in oral doses of 0 3 Gm. daily beginning on the date indicated by the arrow

therapy is followed by moderate reticulocytosis and a gradual rise of hemoglobin level at a rate of 0 1 to 0 2 Gm per hundred milliliters per day The cell volume increases and the hematologic picture returns to normal Figure 4 illustrates the response of a patient treated with 0 3 Gm of ferrous sulfate daily

In view of the considerations which have been reviewed it is not possible to evaluate the benefits of including iron in the enrichment of flour and bread As a matter of fact the evidence is unconvincing that certain of the iron preparations which have been used in

enrichment mixtures actually result in an increase in the amount of absorbable iron in the diet. The importance of the problem of iron deficiency is such that a solid appraisal of the program based on human physiology is needed.

TOXICITY OF IRON

There exists an exceedingly wide range of safety between the therapeutic and toxic doses of orally administered iron. While even ordinary therapeutic doses of soluble iron preparations may produce some gastrointestinal symptoms, these are seldom of much importance. Massive overdosage of iron, however, may produce serious, even fatal, consequences. Thus the ingestion by children of amounts of ferrous sulfate of 6.0 to 10.0 Gm. has produced death with acute hemorrhagic gastritis and liver damage.[37] Ingestion by a 2 year old child of 2.0 Gm. of ferrous sulfate resulted in a severe but not fatal gastritis. Obviously therapeutic iron preparations should be kept out of the reach of small children. From a pharmacologic study of iron preparations Somers[38] has estimated the lethal dose for an adult as at least several hundred 0.2 Gm. tablets of ferrous sulfate.

The parenteral administration of even small amounts of iron (colloidal ferric oxide or colloidal ferric hydroxide) has been termed[39] "impractical, dangerous and unnecessary as a therapeutic measure." It is followed by a febrile reaction, shock and thrombosis of the receiving vein. The toxic symptoms have been described in detail by Goetsch, Moore and Minnich.[39] Nissim,[40] however, has reported on a preparation of "saccharated iron" which it seems may be administered to patients intravenously in quantities supplying up to 500 mg. of elemental iron without these toxic reactions developing. Further development of such preparations may offer feasible parenteral therapy for limited use.

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37. Forbes, G.: Poisoning with a Preparation of Iron, Copper and Manganese, Brit. M. J. 1: 367 (March 22) 1947.

38. Somers, G. F.: Relative Oral Toxicity of Some Therapeutic Iron Preparations, Brit. M. J. 2: 201 (Aug. 9) 1947.

39. Goetsch, A. T.; Moore, C. V., and Minnich, V.: Observations on the Effect of Massive Doses of Iron Given Intravenously to Patients with Hypochromic Anemia, Blood 1: 129 (March) 1946. Heath, C. W.; Strauss, M. B., and Castle, W. B.: Quantitative Aspects of Iron Deficiency in Hypochromic Anemia, J. Clin. Investigation 11: 1293 (Nov.) 1932.

40. Nissim, J. A.: Intravenous Administration of Iron, Lancet 2: 49 (July 12) 1947.

COPPER

Any attempt to arrive at a conclusive statement regarding the occurrence of copper deficiency in man or the human requirements of copper would be most premature and would, therefore be controversial Most of the clinical studies[41] on man which purport to produce evidence of copper deficiency are open to definite criticism Rigidly designed studies on man in this area are badly needed

Certain facts relative to the nutritional role of copper seem indisputable Copper is an essential nutrient for rats and for several other experimental animals A deficiency of the element is manifest by a hypochromic usually microcytic anemia and general debility as well as depigmentation There occurs a decrease in the activities of oxidative enzymes (cytochrome cytochrome oxidase and catalase) in the tissues of deficient rats Herbivora are particularly susceptible to this deficiency, and it may occur under practical feeding conditions especially if a pasture area low in copper has been treated with molybdenum[4] The anemia of copper deficiency is a reflection of the inability to mobilize iron for hemoglobin production

The human diet ordinarily contains 2 to 4 mg of copper per day The metal may be absorbed from the gastrointestinal tract with retention of some 5 to 40 per cent of the intake Balance studies on man reveal that a daily intake of approximately 2 0 mg will maintain adults in balance Such evidence however should not be construed as defining a requirement The copper content of whole blood is approximately equally divided between cells and plasma and usually lies between 90 and 150 micrograms per hundred milliliters for men and 100 and 160 micrograms for women Similar levels are obtained for serum copper—thus Nielsen[43]

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41 The literature on copper metabolism and deficiency is well summarized in the following reviews Schultze M O Metallic Elements and Blood Formation Physiol Rev **20** 37 (Jan) 1940 Schultze M O Some Biochemical Aspects of Metabolism of Iron and Copper Symposia on Nutrition I Nutritional Anemia Cincinnati The Robert Gould Research Foundation Inc 1947 p 99 Cartwright[*] Anonymous Present Knowledge of Iron and Copper in Human Nutrition Nutrition Rev **4** 291 (Oct) 1946

42 Davis G K Mineral Element Deficiencies and Their Influence on the Growth and Nutrition of Animals Proceedings of the Southern Conference on Nutrition and Public Health, School of Public Health, Chapel Hill University of North Carolina Nov 14 15 1947 p 9

43 Nielsen A L On Serum Copper I Introduction Acta med Scandinav **118** 84 (Sept) 1944 III Normal Value ibid **118** 87 (Sept.) 1944 IV Pregnancy and Parturition ibid **118** 92 (Sept) 1944

reports 110 plus or minus 12 micrograms per hundred milliliters for healthy men and 123 plus or minus 16 micrograms for healthy women He noted appreciable diurnal variations in the serum copper values During the latter half of pregnancy there is a definite rise in the copper content of the serum a rise which disappears within one to two months after delivery Serum copper values are low (by adult standards) in the newborn Van Ravesteyn [44] found that giving copper by mouth did not appreciably increase the serum level or the urinary content of the element This latter varied from 0 to 12 5 micrograms per hundred milliliters The administration of copper intravenously resulted in a transitory rise in serum and urinary content but both returned to pretreatment levels within a few hours Biliary and fecal content of copper rose sharply after administration of copper by either oral or intravenous routes It is apparent that copper is excreted by man in the bile and there is a possibility that it is excreted in part by the intestinal wall

Milk is extremely low in copper content The successful production of copper deficiency in rats fed a milk diet has led to the repeated suggestions that infants restricted to milk alone may reveal signs of copper deficiency and that copper is a logical adjunct to iron for therapy of hypochromic microcytic anemia of infants While the evidence indicates that some hemopoietic effect of copper may have been observed in an occasional anemic infant there is need for a definitive study of this claim The point is one which has more practical bearing on the prevention of this anemia than on its treatment, for most infants with hypochromic microcytic anemia respond satisfactorily to the iron preparations in common use

In the adult hypochromic microcytic anemia is due to blood loss, hence it would not be expected that copper deficiency would be encountered The investigations of the hemopoietic effect of copper leave me unconvinced that copper deficiency has been encountered in the adult.

A disease of ruminants known as scouring has long been associated with teart pasture areas The herbage from these areas has been found unusually high in con

44 Van Ravesteyn A. H M tabolism of Copper in Man, Acta med. Scandinav **118**: 163 (Sept) 1944

tent of molybdenum[45] The condition is counteracted by the feeding of copper or by the addition of copper to the soil This antagonism of molybdenum and copper in animal nutrition raises the question of a possibly toxic effect of certain of the pharmaceutic preparations of iron with molybdenum which are now marketed and used in prenatal care[46] This question becomes the more pertinent when it is recalled that there normally occurs a pronounced rise in serum copper in pregnancy and that the fetal (cord) serum is low in copper Will administered molybdenum upset an important metabolic adjustment in copper metabolism? I have been unable to find evidence bearing on this point

ADDITIONAL REFERENCE

Kirch E R, Bergeim O, Kleinberg J and James S Reduction of Iron by Foods in Artificial Gastric Juice J Biol Chem 171 687 (Dec) 1947

45 Stiles W Trace Elements in Plants and Animals 1946 New York The Macmillan Company especially pp 131 135

46 Neary E R The Use of Molybdenized Ferrous Sulfate in the Treatment of True Iron Deficiency Anemia of Pregnancy Am. J M Sc. 212:76 (July) 1946.

CHAPTER VI

IODINE IN NUTRITION

GEORGE M CURTIS
and
M BEEN FERTMAN

During the early years of the past decade, perhaps even in the still turbulent days of 1950 there could be seen on the highways of the Chinese province of Yunnan numbers of cretins as well as other persons little more fortunate, displaying prominent goiters Men and women working on the Burma Road were showing an incidence of thyroid enlargement often as high as 80 per cent[1] Residence in the Yunnan district for as little as six months it appears would suffice to induce such deformity in susceptible persons

Toward a better understanding of this striking phenomenon, in many respects similar to the once epidemic proportion of goiter and cretinism in Berne Switzerland, geologic formation and even the historical evidence might lend some further insight The Japanese were early in the 1940s still in control of strategic areas of China As a consequence the hinterland of China did not have access to the high iodine-containing sea foods Yunnan as well as other large sections of free China, were thus consuming their indigenous foods grown on an iodine impoverished soil and salt from iodine-deficient salt mines In occasional isolated goiter free towns of Yunnan, a dirty grey salt which local superstition held to possess miraculous qualities was being imported from Szechwan, a province with iodine rich salt mines Neighboring goitrogenic villages were found to depend upon their own iodine poor supplies[1]

In considering the problem of endemic goiter in Yunnan province as a whole one is inclined to the view that the basic trouble is lack of iodine in the locally grown foodstuffs The reason is that the surface soils

[1] Robertson R C The Problem of Endemic Goiter in Yunnan Province J Clin Endocrinol. 1:285 1941

have all had the very soluble iodides washed out either in the mountain rivers or into deeper subsoil not reached by the small plants "[1] The inverse relation between a high incidence of goiter and cretinism and the amount of iodine found in the soil of a given region in its water, its salt and mineral deposits, and particularly in its food has long been known Repeatedly this observation has been supported by similar evidence

Thus it becomes necessary to appreciate the powerful role which iodine plays in human biologic processes This element is found throughout the world in varying proportions It occurs in minute quantities in the very air one breathes It is dispersed in the water It exists in the soil and in the rocks It is present in nearly all living things, both plant and animal Not the sea as is popularly believed but the earth's crust is the major storehouse of iodine[2]

Endemic goiters are observed in numbers among the inhabitants of those regions deficient in iodine The highest incidences of goiter have been observed in the Alps the Pyrenees and Himalayas the Thames Valley in England certain inhabited districts of New Zealand in the region of our own Great Lakes and in the Pacific Northwest[2b] Throughout the United States there occur varying degrees of available iodine depending on local geologic conditions of the soil and waterways A high incidence of goiter is especially noteworthy in the Central Plain of North America, where regional iodine is low On the sea coasts where large amounts of high iodine containing sea foods are consumed, there is a minimum of endemic goiter

The water of the Great Salt Lake resembles the ocean in its iodine concentration and yet unlike the ocean supplies neither vegetation nor fish for human consumption[2b] Consequently it should cause no great wonderment that the inhabitants of the Great Salt Lake area have a high incidence of goiter for the problem of endemic goiter largely resolves itself into a consideration of the amount of mammalian iodine consumption within any given region

Iodine is ingested essentially from the food supply and to a lesser degree from ordinary salt or from

2 (*a*) Orr J B and Leitch I Iodine in Nutrition Medical Research Council, Special Report Series No 123 London His Majesty's Stationery Office, 1929 (*b*) McClendon J F Iodine and the *Incidence of Goiter* Minneapolis University of Minnesota Press 1939

water[2a] About 14 micrograms daily was formerly thought to represent the difference in iodine intake between goitrogenous and nongoitrogenous regions[3] However regional differences in iodine consumption have become even less pronounced as the interstate transportation of food drinks vegetables fruits and fertilizers has increased

The amount of iodine found in the local drinking water is not important as a source of nutritional iodine save in unusual circumstances[3] Nevertheless, it is a frequently used index of the iodine content of the regional soil and consequently of its vegetables fruits grains and grasses Moreover when the country is divided into sections according to the occurrence of iodine within its waters, it will be found that where the iodine content is low the incidence of goiter is correspondingly high Such regions are to be found in a section extending from Oregon to the western part of Maine and from Nevada to the western part of Virginia[2b] The Michigan studies revealed that the incidence of goiter in a given locality varies inversely with the amount of iodine found in its water[4]

The iodine content of the food is an important factor determining the extent of endemic goiter prevalent throughout a given area Thus it is readily understood why Japan though geologically low in iodine presents an outstanding example of a goiter free area while Formosa similarly depleted in iodine has a high incidence of goiter among its population The absence of goiter in Japan results from a Japanese taste for seaweed which is therefore extensively imported and consumed in large quantities[2b] Seaweed is unusually rich in iodine content

In South Carolina where the vegetables are considerably higher in iodine content than those of the Northern and Western states the incidence of goiter is low[5] However the interstate importation of canned foods and other food products does not to any apparent degree help solve the goiter problem in the North and West

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[3] Hercus C E and Roberts K C The Iodine Content of Foods, Manures and Animal Products in Relation to the Prophylaxis of Endemic Goiter in New Zealand J Hyg 26:49 1927

[4] (a) Report of the Initial Meeting of the Study Committee on Endemic Goiter of the American Public Health Association Detroit June 14 15 1941 (b) Study of the Effect of the Use of Iodized Salt on the Incidence of Goiter First Official Report of the Goiter Survey of Michigan J Michigan M Soc 36:647 1937

[5] Weston, W Foods in the Solution of the Goiter Problem South. M J 23 479 1930

for the cotton growing and tobacco growing South as a *whole*, comprising a great part of the goiter free United States[6] fails to produce sufficient food and feed crops even for its own needs[6b] Canned goods must therefore be imported from sections of the country where the soil is poor in iodine[6]

The iodine concentration of the milk produced in a given locality is another good index of endemic goiter *in that region*[7] The *amount of iodine which the* lac tating mammal consumes and then puts out in her milk in the absence of any supplemental iodine depends on the amount of iodine in the soil and its vegetation[8] Likewise the egg is dependent on the chicken for its iodine content and the chicken on the products of the "good earth"[7b]

IODINE CONTENT OF THE HUMAN BODY

A normal man weighing 70 Kg may be reasonably estimated to contain about 50 mg (less than a grain) *of iodine This is equivalent to about* 1 part in 1,400 000 of body substance Iodine thus forms less than 0 00008 of 1 per cent of the total body weight Nevertheless every cell in the body is said to contain some iodine[9]

IODINE AND THE NORMAL THYROID GLAND

The thyroid gland is a principal storehouse for the iodine of the human body Weighing ordinarily about 25 Gm and containing about 10 mg of iodine, it normally maintains an iodine concentration of around 40 mg per hundred grams It was shown long ago by Marine and Lenhart that when this concentration falls below 10 mg per hundred grams hyperplasia ensues and goiter is likely to develop[10]

No other organ of the mammalian body has the power of iodine concentration possessed by the thyroid gland

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6 (*a*) McClendon [b] (*b*) Olesen R Endemic Goiter Public Health Bulletin 19 Washington D C Government Printing Office 1929 p *27* Opportunity or Calamity editorial Food Industries *3*: *467* 1931

7 (*a*) Orr and Leitch [8a] (*b*) Shore R A, and Andrew R L Goiter in School Children The Incidence of Goiter in School Children in Relation to the Amount of Iodine in Soil and Water in Certain Districts of the North Island in New Zealand Bull Hyg 5 94 1930

8 (*a*) *Shore and Andrew* [7b] (*b*) *Meyer J H The Iodine Con*tent of Milk Thesis Columbus Ohio Ohio State University Department of Surgical Research 1940

9 Justus J Ueber den physiologischen Jodgehalt der Zelle Virchows Arch f path Anat. **170**: 500 1902

10 Marine D and Lenhart C H Further Observations of the Relation *of Iodine* to the Structure of the Thyroid Gland in the Sheep Dog Hog and Ox Arch Int Med **3**: 66 1909

The whole blood iodine averages less than 1 part in 25 000 000 while the thyroid gland normally contains approximately 1 part in 2,500 This indicates that the thyroid gland can concentrate the iodine it obtains from the blood by a factor of at least 10 000

Within the colloid in the alveoli of the thyroid gland iodine is stored in a combined form with the amino acids diiodotyrosine and thyroxine These contain respectively, 59 and 65 per cent iodine The accepted facts of thyroid function indicate that iodine is selectively absorbed by the active thyroid gland Furthermore in some measure the glandular function is regulated by its iodine content Studies with radioactive iodine have shown that ingested iodine is quickly brought to the gland by the blood stream and rapidly converted by the thyroid cells into complex organic compounds Within a matter of only a few hours these organic iodine compounds just manufactured by the cellular activity of the thyroid gland may return to the circulation [11]

A basic peculiarity of this regulating gland, first observed before the turn of the century [12] is its low iodine concentration when its weight is high and inversely a high iodine concentration when its weight is low [13] Moreover, the thyroid iodine content is low with either a high incidence of nodule formation or a high percentage of epithelial proliferation It is low with increased height of the follicular epithelium of the thyroid gland, lymphocytic infiltration and with the occurrence of degenerative changes [13b]

The iodine which a person absorbs from his daily food is the principal factor which determines the iodine content of the thyroid gland and overshadows other factors such as species age and sex Small differences in the local food supply of iodine are reflected in the iodine content of the gland [2a]

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11 Perlman, I Chaikoff, I L. and Morton M E Radioactive Iodine as an Indicator of the Metabolism of Iodine I The Turnover of Iodine in the Tissues of the Normal Animal with Particular Reference to the Thyroid J Biol Chem 139 433 1941 Perlman, I, Morton M E and Chaikoff I L II The Rates of Formation of Thyroxin and Diiodotyrosine by the Intact Normal Thyroid Gland ibid. 139: 449 1941

12 Baumann E Ueber den Jodgehalt der Schilddrusen von Menschen und Thieren Ztschr f physiol Chem. 22: 1 1896

13 (a) Marine David and Lenhart.[10] (b) King J D The Iodine Content of the Normal Thyroid Gland Correlated with Its Histology and the Iodine Content of Other Normal Body Tissues in Central Ohio Dissert Columbus Ohio Ohio State University Department of Surgical Research 1940

Since iodine intake is so largely dependent on the soil and consequently on plant iodine, the thyroid iodine concentration varies with the geographic distribution of iodine Thus, in nongoitrogenous Texas the fat free dried thyroid contains on an annual average, 6 mg of iodine per gram whereas in goitrogenous North Dakota it contains only 3 2 mg per gram [14] There are seasonal variations in the amount of iodine found in the thyroid gland [15b] but these may be attributed to seasonal variations of the iodine available in the soils and food stuffs

IODINE AND THE PATHOLOGIC THYROID GLAND

The ultimate cause of endemic goiter and its sequelae is not clear An immediate cause is a deficiency of iodine, an element necessary in the production of the thyroid hormone with its high content of iodine This iodine deficiency may be absolute, as in areas where the iodine intake is subnormal, or the deficiency may be relative [15] Thus iodine deficiency may ensue, even with a normally adequate iodine intake whenever gastrointestinal absorption is inadequate Other uncompensated circumstances by interfering with the normal destination and metabolism of iodine, or by increasing the demand for this element have the same end result Infectious processes the ingestion of toxic substances or of certain drugs and a diet high in calcium are among the known offenders Certain foods have been shown to contain goitrogenic substances [16a b] The physiologic stress of puberty of pregnancy and of lactation increases the need for thyroid secretion When these increased needs are met with an increased supply, resultant pathologic change is forestalled as can be demonstrated in the thyroid histologic observations in pregnant animals fed sufficient supplemental iodine [17]

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14 Fenger F Andrew R. H and Vollertson J J Geographic Location and the Iod ne Content of the Thyroid Gland J Am Chem Soc **53** 237 1931

15 Elmer A W Iodine Metabolism and Thyro d Function London Oxford University Press *1938*

16 (*a*) Greer M A Ettl nger M G and Astwood E B D etary Factors in th Pathogen sis of S mple Go ter J Cl n Endocr nol **9** 1069 1949 (*b*) Gr er M A and Astwood E. B The Antithyro d Effect of Certain Foods n Man as Determ ned by Rad o ct ve Iod e Endocrinology **43** 105 *1948* (*c*) *Curt George M and Swens n R E Thiou acil* and Its All es in the Treatment of Hype thyro d sm Surg Gynec. & Obst. **86** 105 1948

17 Schmeling J W Over de normale en vergroote Sch ldkl er geduren de embryonale outwikkel ng bij den pa geb rene en pasgeborene en bij het jonge *Kind in Nederland D ssert Utrecht 1934*

Considerable importance has been attached to the role played by the liver with respect to iodine.[24] Nevertheless, its actual function in this regard is still an enigma The conviction that this significant organ, which affects so many of the body's vital activities, also exerts an influence on the metabolism of iodine, arises from various experimental and clinical observations Thus, bile is consistently high in iodine content,[22] and except for the thyroid and hair contains, in fact the highest iodine concentration in the human body [22] Moreover elevation of the blood iodine, occasionally to a considerable degree has been observed in patients with hepatic damage and in those with biliary tract disease [24b] Recent investigation suggests a possible relationship of these phenomena to a newly found 'antithyrotoxic" factor in liver, which presumably is a direct antagonist to the usual action of the thyroid hormone.[25]

The amount of iodine in the blood has for many years merited special consideration It is an index of thyroid function and of iodine metabolism It is a rough measure of the release of the thyroid hormone and of its rate of breakdown within the body after it has completed its function With radioactive tracer methods, this significance has become even more clear With improving technics in the fractionation of the blood and plasma iodine, means of distinguishing the circulating thyroid hormone from its breakdown products are emerging [26] Meanwhile studies of the whole blood iodine and particularly of the protein bound fraction serve along with determinations of basal metabolic rate to differentiate the various thyroid diseases from each other and to distinguish them from normal and nonthyroid clinical states

Human blood normally maintains a fairly constant level of iodine Fractionation studies reveal that about one fourth of this presumably represents the circulating

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24 (a) Elmer [16] (b) De Courcy, J L. Iodine Metabolism Normal and Abnormal Its Relation to the Reticulo-Endothelial System Tr Am A. Study of Goiter 1937 p 133 Further Study of Blood Iodine Changes in Affections of the Gallbladder Surg Gynec & Obst 65: 180 1937 Iodine Content of Blood in Cholecystic Disease Arch Surg 35: 140 1937

25 Betheil, J J Wiebelhaus V D and Lardy H A A Nutritional Factor Which Alleviates the Toxicity of Ingested Thyroid Substance J Nutrition 34: 431 1947

26 Curtis G M and Swenson R E The Significance of the Protein bound Blood Iodine in Patients with Hyperthyroidism Ann Surg 128 443 1948

turnips, cabbage, kale and rape, as well as from the *seeds* of the *Brassicae* Experimentally, it is one fifth as active as thiouracil, and slightly more active than propyl thiouracil in man Except for rutabagas and white turnips however the *edible* portions of other members of the cabbage family have not shown any detectable thiooxazolidone It has been speculated that the goitrogenic substance in cabbage may be different since adding sufficient iodine to the diet will completely inhibit the development of "cabbage goiter," whereas it only partially inhibits the *Brassica* seed type of goiter Other vegetables have shown an 'antithyroid' activity in animals,[19a b] and in man [18b] These substances, how ever, have been shown to produce goiter only when given persistently and in abnormal amounts

IODINE IN THE EXTRATHYROID TISSUES AND BODY FLUIDS

Iodine is present in organs other than the thyroid gland It is also found in varying concentration in other body tissues and in the various body fluids Its role there is less clearly understood Of the total iodine content of the human body about one half can be assigned to the muscles, one fifth to the thyroid one tenth to the skin and one seventeenth to the bones [20]

Because of the close interrelationship of the other endocrines with the thyroid gland, their iodine content becomes even of practical interest There is some ques tion whether they actually exceed the nonendocrine tissues in iodine concentration Certain studies indicate that they do [21] More recent work on mammalian tissue iodine [18b] and on the iodine content of normal human tissues [2] *was not confirmatory Moreover, the* master gland," the pituitary which bears a reciprocal relation to the thyroid so well appreciated, has a low iodine content This is similarly true of the central nervous system itself [23]

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19 (*a*) *Wagne Jauregg T and Koch J Ern hrungsbedi gte* Sch ld drusenstorungen beim Kan nchen Wien Klin Wchnschr **58** 448 1946 (*b*) Sharples G R A New Goiter Produc ng Diet for the Rat, Proc Soc Exper Biol & Med **38** 166 1938

20 Sturm A and Buchholz B Jodverteilung m men chl chen und tierischen Organ smus n hrer Beziehung zur Schilddruse Deutsches Arch f klin Med. **161** 2 7 1928

21 Sturm and Buchhol [20] von Fellenbe g T Versuche uber die Jodspe cherung n den e n elnen Org nen Biochem Ztschr **174**: 355 19 6 Maurer *E and Ducrue H Zur Kenntn s des Jods* als biogenes Element, ibid. **217**: 227 1930

22 Libecap I L The Iod ne Content of Normal Human Tissues Thesis Columbus Ohio Ohio State Unive s ty Department of Surgical Research 1942

23 King [18b] Libecap [22]

between the blood iodine and the basal metabolic rate in thyroid disease, noted particularly in those goitrous conditions associated with hyperthyroidism[31b] as well as in nontoxic nodular goiter[32]

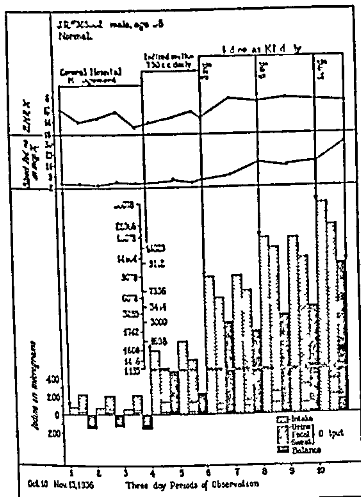


Fig 1.—Chart showing levels in a normal subject for three day periods of observation

Thyroidectomy, in human beings or in experimental animals, exerts an important effect on the blood iodine Immediately following total thyroidectomy there is a transient increase in the blood iodine, which persists for about thirty six hours Following total thyroidec-

32 Curtis and Swenson,[30] Curtis and Fertman[31b]

thyroid hormone.[27] The other three fourths, consequently would include the iodine of nutrition together with products of the breakdown of the thyroid hormone with its high content of iodine

Various values, ranging from 3 to 20 micrograms per hundred cubic centimeters, have been ascribed by different investigators to the normal iodine level in whole blood [8] These vary with the method of iodine determination and the geographic area, as well as with certain physiologic factors The blood iodine is significantly increased in pregnancy, in parturition and in toxic nodular and exophthalmic goiter (fig 3) as well as in certain nonthyroid diseases [9] Increased blood iodine levels observed in toxic nodular and exophthalmic goiter may be due, in part, to iodine medication, for the administration of iodine in all forms increases the circulating iodine in whole blood (fig 1) [30]

In hypothyroidism, the iodine in whole blood is often within normal limits [29b] Nevertheless, the acetone-insoluble fraction, which presumably contains the circulating thyroid hormone, has an average value of about one-half normal [27a] In nontoxic nodular goiter, this fraction may show an increase over normal [6] when the whole blood iodine does not [29b]

The iodine concentration in the blood varies, however, it maintains a more constant level than the iodine in the thyroid [15] The whole blood iodine does not always increase or decrease along with the basal metabolic rate.[31] The latter is less exclusively controlled by the thyroid gland than the circulating iodine and is in fact, the resultant of a number of different metabolic processes However there is a significant correlation

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27 (a) Dawson, R A Zollinger R W and Curtis, G M The Fractionation of the Blood Iodine J Lab. & Clin. Med. 27:643 1942 (b) Curtis and Swenson [illegible]

28 Davis, C. B Curtis, G M and Cole V V The Normal Iodine Content of Human Blood J Lab. & Clin. Med. 19:818, 1934

29 (a) Curtis, G M Cole V V and Phillips F J Blood Iodine in Thyroid Disease West. J Surg 42:435 1934 (b) Curtis, G M., and Fertman M B An Analysis of the Blood Iodine in Thyroid Disease, Arch. Surg 50:207 (April) 1945 (c) The Blood Iodine in Nonthyroid Disease ibid 54:541 (May) 1947

30 (a) Orr and Leitch [illegible] (b) Elmer [illegible] (c) Salter W T Endocrine Function of Iodine Cambridge Mass. Harvard University Press, 1940. (d) Curtis, G M Iodine Metabolism in Toxic Goiter J Med. 15:148, 1934

31 (a) Curtis and Fertman [29b] (b) Curtis, G M and Fertman, M B The Relation of the Basal Metabolic Rate to the Blood Iodine in Thyroid Disease, Ann. Surg 122:963 1945

exudates and in milk In milk it plays the important role of supplying the needed iodine to the growing infant. This iodine is lost at the expense of the mother's iodine stores [1b] and should be replaced, to maintain the

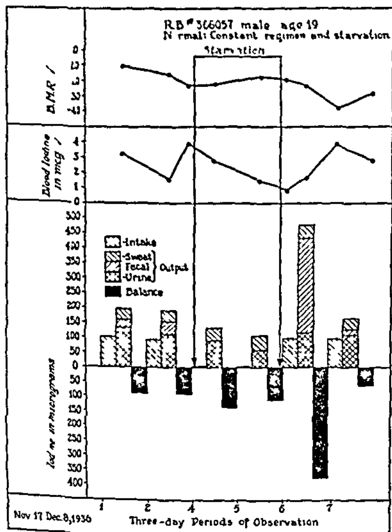


Fig. 2—Chart showing levels in a normal subject during a constant regimen and starvation in three day periods of observation

health both of the child and of its mother If iodine feeding is essential under normal conditions of stress and strain, then it is twice as important to the woman who bears a developing fetus or to the lactating mam-

tomy the blood iodine decreases to about one third normal[33]

The urinary iodine is another measure of iodine metabolism Under maintained basal conditions, together with a monotonous diet low in iodine, the normal adult excretes a surprisingly constant amount of iodine in the urine[34] (figs 1 and 2) There is, however, geographic variation The urinary iodine is higher in sea coastal regions than inland regions[18] It is higher in the non goitrogenous than in goitrogenous areas, as illustrated by the contrasting range in iodine excretion of 72 to 343 micrograms a day observed in five nongoitrogenous regions and of 27 to 64 micrograms a day in five goitrogenous districts The average twenty four hour urinary iodine excretion by normal adults in Central Ohio, a region of moderate endemic goiter, is 51 micrograms[35]

Several factors tend to increase the amount of iodine lost in the urine These include hyperthyroidism (fig 3),[36] menstruation,[37] pregnancy,[38] surgical treatment[39] and the administration of iodine in nearly all forms (fig 1)[40] On the other hand, fasting decreases the urinary excretion of iodine (fig 2)[40b] The decrease is less when the fasting is preceded by an iodine rich diet[30c]

Iodine is also present in other body fluids It has been demonstrated in the lymph, in cerebrospinal fluid in perspiration (fig 3), in chyle, in ascitic fluid, in pleural

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33 Curtis G M Barron L E and Phillips F J The Blood Iodine After Total Thyroidectomy in Man J Lab & Clin Med **20**: 813 1935

34 Curtis G M Puppel I D Cole V V and Matthews N L The Normal Urinary Iodine of Man J Lab & Clin Med **22**: 1014 1937

35 (a) Curtis Puppel Cole and Matthews[34] (b) Curtis G M and Puppel I D Urinary Iodine in Thyroid Disease West. J Surg **45**: 417 1937

36 Curtis G M and Puppel, I D Increased Urinary Excretion of Iodine in Hyperthyroidism Arch Int. Med **60**: 498 (Sept) 1937

37 Cole V V and Curtis G M Cyclic Variations in Urinary Excretion of Iodine in Women Proc Soc Exper Biol & Med **31**: 29 1933

38 Enright L Cole V V and Hitchcock F A Basal Metabolism and Iodine Excretion During Pregnancy Am J Physiol **113**: 221 1935

39 Curtis and Puppel[35b] James A G The Postoperative Loss of Iodine in the Urine Thesis Columbus Ohio Ohio State University Department of Surgical Research 1937

40 (a) Footnote 35 (b) Curtis G M and Puppel I D The Iodine Metabolism in Thyroid Disease Tr Third Internat. Goiter Conference, Washington D C 1938 p 367 The Iodine Metabolism in Exophthalmic Goiter Ann Surg **108**: 574 1938

preparing war materials for Napoleon. Within a few years Sir Humphrey Davy had isolated iodine from sponges, seaweed and other forms of marine life. Then followed a fruitful century of clinical investigation, extending from Straub of Berne to Plummer of Rochester, and of fundamental experimental researches, dating from Boussingault of Paris through Chatin, Baumann, Kendall, Marine, von Fellenberg and others to Harington of London.

Today iodine prophylaxis against goiter is widely recognized while iodized salt is used throughout the entire United States. The extensive and increasing popularity of the use of iodized salt started from the original experiments conducted in Akron, Ohio.

Marine and Kimball's significant studies on the prevention of goiter were made on a large group of school girls.[43] About one half voluntarily received 200 mg. of sodium iodide daily for a period of two weeks each spring and fall. Among almost 4,500 girls who showed no evidence of goiter at the time the experiment was instituted, in 21.5 per cent of those without iodine supplements, and, on the other hand, in only 0.2 per cent of those who received iodine, enlarged thyroid glands developed during the two and one half years of observation.

More than 2,000 of the Akron school girls showed an initial thyroid enlargement. In as many as 65.4 per cent of those receiving iodine there occurred a reduction in the size of the thyroid gland at the end of one year. Only 13.8 per cent of the untreated girls showed any diminution in the size of their goiters. This same study revealed that goiter is most likely to develop during fetal life, during puberty and during pregnancy.[43]

The character and results of the Ohio demonstration stimulated similar efforts throughout the world, particularly in Switzerland, Austria and Germany. Iodine prophylaxis in Switzerland brought the steady decline of cretinism, so important an economic factor to the Swiss. Until 1922 every other newborn infant in the Canton of Appenzell began life with an enlarged thyroid gland. With the institution of iodized salt this morbidity among newborn infants definitely diminished. Moreover, as a result of the efforts of the Swiss Goiter

43 Marine, D., and Kimball, O. P.: Prevention of Goiter in Man, J. A. M. A. 77: 1068 (Oct. 1) 1921.

mal The loss of iodine in milk results in depletion of the mother's iodine reserve with an ensuing negative iodine balance[40b] This loss should be compensated for by a sufficiently large iodine reserve, previously built up, or by an increased iodine intake[41] As iodine is administered to the mother, a greater proportion of this substance will be secreted in the milk[42]

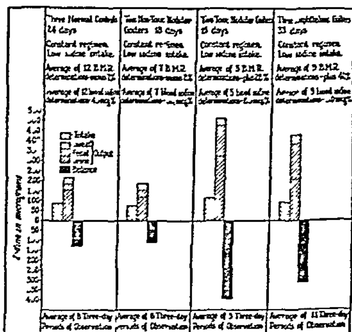


Fig 3—Chart showing levels seen in three day periods of observation for normal subjects and patients with various types of goitrous conditions.

IODINE AND THE PREVENTION OF GOITER

Fortunate was the empiricism which led the ancients to use burnt sponge or seaweed in the treatment of goiter Iodine was unknown It was not until 1811 that iodine was accidentally discovered by Courtois as a by product resulting from the use of seaweed ash in

41 Elmer[38] Marine, D Studies on the Etiology of Goiter Including Graves Disease, Ann. Int. Med. 4 423 1930 The Importance of Relative Iodine Deficiencies in Certain Forms of Goiter J Am. Dietet. A. 9 1 1933

42. (a) Meyer[40] (b) Matthews, I L. Curtis, G M., and Meyer J H. The Effect of Increased Iodine Feeding on the Iodine Content of Cow's Milk, J Dairy Research 10 395 1939 (c) von Fellenberg, T Das Vorkommen, der Kreislauf und der Stoffwechsel des Jods, Ergebn. d. Physiol. 25 1 6, 1926

The efficacy of iodine prophylaxis is greater the earlier it is applied and decreases after puberty.* Consequently it would seem wisest to commence prophylaxis even before the time of conception and to maintain it throughout the pregnancy. It should be continued during childhood and particularly through the menarche. This can be adequately accomplished in iodine deficient regions where goiter is frequent by the continued use of iodized salt.

Subsequent to the nearly worldwide preventive use of iodine a general decline in the incidence of goiter occurred particularly in Switzerland, in Austria, Germany, Northern Italy, the United States, England, New Zealand in Poland, Rumania and Latvia.[18] A turn-about in the incidence of goiter in those countries ravaged by war may be anticipated along with other nutritional deficiency diseases now rampant in Europe and in Asia. As iodine deficiency develops, the incidence of endemic goiter will increase.

Despite almost worldwide favorable results with iodine prophylaxis, thus again substantiating the basic theory on which it rests, objections have been repeatedly raised, in the earlier years abroad and more recently in the United States, to the preventive use of supplemental iodine. Principal among these objections has been the conjectured harm which iodine might inflict on persons with overactive thyroid glands. Moreover, there has been concern that a simple nodular enlargement of the thyroid might thus be stimulated so that a "toxic" or hyperfunctioning type of condition developed.

The basis of this fear of "jodbasedow" or iodine-induced hyperthyroidism, arose as early as 1820, when Coindet treated his patients with excessive amounts of iodine.[46] This fear has continued through the years almost paralleling the subsequent progress and repeated successes of iodine prophylaxis. It has been a natural reaction to the dangers inherent in pioneering a drug the action of which was not fully understood. More recent exponents of the theory behind "jodbasedow" were Theodore Kocher and his successor Fritz de Quervain. In 1904 Kocher reported that hyperthyroidism may develop in patients with nodular forms of goiter

46. Coindet, J. R. Decouverte d'un nouveau remede contre le goitre, Ann. de chim. et phys. 15: 49, 1820.

Commission, the use of iodized salt in the Canton of Vaud reduced the community's total goiter incidence from 77 to 21 per cent in fifteen years[44]

The results of the incorporation of iodine in the salt consumed in the state of Michigan were likewise convincing In 1924 common salt iodized to contain 0 02 per cent of sodium iodide was introduced by the Iodized Salt Committee of the *Michigan State Medical Society* in cooperation with the State Board of Health From that year on to 1935 there ensued a 75 to 90 per cent decline in the incidence of goiter in those counties using the iodized salt[4b] The number of goiter operations in seven large hospitals in Southern Michigan dropped from 1,452 in 1927 to 591 in 1933[45] There was a 60 per cent decrease in the number of goiter operations performed as compared with the 17 per cent decrease in all operations during the corresponding depression years

Iodine supplementally administered in the form of iodized salt has repeatedly proved beneficial in the *prevention of endemic goiter* *Its curative effect* however depends on the character of the goiter as well as on the age of the patient at the time iodine therapy is instituted While iodine administration is of value to patients with colloid goiter[a] little beneficial change may be expected in older patients with goiters of long standing in which there are extensive pathologic alterations, such as hemorrhage with resultant cyst formation calcification vascular degenerative changes and old nodular formations[30a b]

Ordinarily microscopic changes will occur in hyperplastic thyroid glands after the administration of supplemental iodine Rapid involution of existing hyperplasia may be induced Moreover, glandular hyperplasia of the residual tissue even after extirpation of as much as three fourths of the thyroid, can be prevented by the administration of sufficient iodine It has been observed that a hyperplastic gland cannot revert to the colloid state without the presence of a necessary minimum of iodine[10]

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44 Eggenberger H Kropf und K et nismus in H rsch M Handbuch der nneren Sekretion Leipz g Curt Kab tzsch 19.7 vol 3 pp 3 and 4

45 McClure R D Thyro d Surgery in Southern M chigan as Affected by the Generalized Use of Iodi d Salt J M ch gan M Soc **33** 58, 1934 The Incidence of Oper tions for Go ter in Southern Michigan Effect of Iodized Salt After Twelve Years General Use, J A. M A. **109**: 782 (Sept. 4) 1937

ensuing from iodine deficiency are in great part the result of the importance of iodine in maintaining normal thyroid function

Sufficient iodine is requisite for normal growth It is well known that thyroid substance plays this role. As early as 1895 it was demonstrated that growth may be induced even in certain cretins by the administration of dried thyroid Similar results have since been obtained in children of iodine deficient areas, who have failed to grow normally because of lesser degrees of hypothyroidism [51] Topper and Cohen recorded that the administration of thyroid to normal children, as well as to children presenting evidence of hypothyroidism, resulted in definite growth acceleration in both groups [52]

The role of iodine in growth has also been demonstrated Thus Swiss statistics show that boys receiving supplemental iodine grew in a year on the average 7 mm more than untreated boys and put on 200 Gm more of weight The mean weight at birth of infants whose mothers were receiving iodized salt was 100 Gm greater than that of control infants [8] Hunziker observed that the average height of Swiss recruits was significantly greater from 1908 to 1912 than during the period from 1884 to 1891 He concluded that supplemental iodine was partly responsible for this increase in stature Moreover he found the average height of recruits from sections with a low incidence of goiter exceeded that of recruits from the more goitrogenous areas [53]

Feeding milk with an increased iodine content to children living in a region of high goiter incidence resulted in more rapid and regular growth and development. Children with debility or those who revealed slow development failure to gain weight or retarded growth showed subsequent steady improvement [54] Administration of optimal amounts of iodine to nursing animals accelerated the rate of growth and weight of

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51 Moore, M C and Moseley H W Iodine and Its Relation to Health New Orleans M & S J 86 449 1934

52 Topper A. and Cohen P Effect of Thyroid Therapy on Children, Am. J D Child 35 205 1928

53 Hunziker H Kropf und Langenwachstum Schweiz. med. Wchnschr 50:209 1920

54 Weston W Specially Produced Milk in the Solution of the Goiter Problem, South. M J 27:249 1934

treated with iodine. In 1910 he wrote of the untoward effects of iodine in toxic diffuse goiter[47] In 1933 de Quervain listed 33 cases of "jodbasedow" observed during a period of nine years[48]

Convincing proof is lacking that iodine induced hyperthyroidism ordinarily or even commonly results from the administration of increased amounts of iodine to goitrous patients On the other hand, evidence is extensive that supplemental iodine is almost universally beneficial in the prevention of endemic goiter Kimball observed that only 4 per cent of patients with "adenomas" had hyperthyroidism after the use of iodized salt, whereas 56 per cent of those with goitrous 'adenomas" who used no iodized salt or any other form of iodine medication later manifested evidence of increased thyroid activity[49]

In current medical practice there is ordinarily little hesitancy in prescribing relatively large amounts of iodide on specific indications syphilis, hypertension or bronchiectasis, for example, without any special regard to the thyroid and its activity Demonstrably harmful effects as a result of increased thyroid function are not expected and are rarely encountered. At most there ensues, from the administration of iodides and then only on occasion, the symptoms of iodism ranging from mild coryza or moderate acne to severe dermatitis accompanied even with a high temperature[30c]

No ill results should be anticipated from the widespread use of iodides in the minute concentration in which they occur in iodized salts, there have been no reports of iodism induced by the consumption of diets rich in iodine-containing foods in the annals of medicine[50]

IODINE IN THE GENERAL HEALTH OF HUMAN BEINGS AND DOMESTIC ANIMALS

Iodine forming 65 per cent of the thyroid hormone is a nutritional necessity for the general health of human beings and domestic animals General health problems

47 Kocher T Die Therapie des Kropfes Deutsche Klin. 8 1115 1904 Ueber Jodbasedow Arch. f klin. Chir 90:403 1910

48 de Quervain, F Report of the Second International Goiter Conference Berne, 1933 pp 10 12

49 Kimball, O P The Efficiency and Safety of the Prevention of Goiter J A. M A. 91 454 (Aug 18) 1928 The Prevention of Goiter in Michigan and Ohio ibid. 108 860 (March 13) 1937

50 Weston, W Iodine in Nutrition, Am. J Pub Health 21:715 1931

Iodine prophylaxis of iodine deficiency disease among domestic animals, or "fetal athyrosis," as it was then designated has spread to other states and provinces Minnesota, North and South Dakota, Wyoming, Washington Idaho, Southern Alberta and British Columbia have similarly used iodine preventively

THE HUMAN REQUIREMENT OF IODINE

The supply of iodine necessary to answer the needs of the human body should be sufficient to meet the daily losses by excretion and to maintain within the body such reserves as may be needed in the manufacture and distribution of adequate thyroid hormone. The amount of iodine intake, however, is not always equal to the physiologic needs This is in contrast with the organism's chlorine requirement which is more easily met because of the association of this element with the sensation of taste

The fundamental question thus arises How much supplemental iodine is necessary in those areas in which goiter is prevalent in order to protect the populace from the effects of iodine deficiency? Thus far, three methods have been developed in attempts to answer this question

By the *geographic method* the iodine intake of the inhabitants of goiter free areas is determined and compared with that of areas of varying degrees of goiter incidence The difference in the amount of average iodine intake is then regarded as the amount of supplemental iodine required According to von Fellenberg's estimate the annual iodine intake in one goitrous and one practically goiter free area in Switzerland was 4 7 and 11 4 mg respectively Calculating from this the iodine requirement would be less than 20 micrograms daily a figure now regarded as extraordinarily low [42c] Calculated on determinations of the average daily urinary loss of iodine (figs 1 and 2) which is an unusually accurate barometer of the iodine intake of a given area the daily iodine requirement would lie somewhere between 100 and 200 micrograms [34]

The principle of *thyroxine formation and decay* was originally outlined by Plummer and Boothby [60] and sub-

60 Plummer H S and Boothby W M Specific Dynamic Action of Thyroxin Am J Physiol 55:295 1921 Plummer H S The Interrelationship of Function of the Thyroid Gland and of Its Active Agent, Thyroxin in the Tissues of the Body J A M A 77:243 (July 23) 1921

their young[55] Direct iodine administration to the young was likewise beneficial[56]

The favorable effect of iodine on the growth of vertebrates may be direct or indirect It appears more likely that iodine acts indirectly by supplying the necessary constituent for normal thyroid secretion, thus permitting the gland to exert its usual function

Besides its importance in growth, iodine also plays a role in human and animal fertility[57] and even in lactation[58] A preliminary report on the effect of iodine on failing lactation indicates that this condition is due not to a defective thyroid gland but to a deficient intake of iodine As in similar experiments with animals[57] all mothers responded with increased output of breast milk[58b]

Breeding difficulties among animals long existed in varying degrees throughout the goiter areas of the United States, until the prophylactic use of iodine became widespread as a means of combating this problem[59]

As early as 1907 iodine-containing salts were fed to Michigan sheep in order to prevent the high mortality rate ordinarily occurring among newborn lambs[59d] In 1916 Montana faced with a high mortality rate among its live stock, as well as with the development of goiter and underfunctioning thyroids, instituted similar treatment with success[59e] Since the introduction of iodized salt at the University of Wisconsin farms in 1920, there has not been an instance of goiter among the domestic animals, including sheep swine colts and calves[44]

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55 Orr and Leitch[34] Maurer E. and Diez, S Ueber Wachstumsbechleunigung an jungen Ratten bei Verfutterung jodar gereicherter Kost an das laktierende Muttertier Biochem Ztschr **182** 291 1927

56 Hanzlik P J Talbot, E P and Gibson E E Continued Administration of Iodine and Other Salts Comparative Effects on Weight and Growth of Body Arch Int. Med **42** 579 (Oct) 1928

57 Phillips F J Erf O and Curtis G M The Effects of Prolonged Increased Iodine Feeding Ohio J Sc. **35** 286 1935

58 (*a*) Phillips Erf and Curtis[*] (*b*) Robinson M Hormones and Lactation Dried Thyroid Gland Lancet **2**: 385 1947

59 (*a*) Smith G E Iodine Requirement in the Pregnant Sow (Fetal Athyrosis) J Biol Chem **29** 215 1917 (*b*) Hart E B and Steenbock H Thyroid Hyperplasia and the Relation of Iodine to the Hairless Pig Malady ibid **33**: 313 1918 (*c*) Kalkus J W A Study of Goiter and Associated Conditions in Domestic Animals Bulletin 156 Washington State Experiment Station July 1920 (*d*) Marine D On the Occurrence and Physiological Nature of Glandular Hyperplasia of the Thyroid (Dog and Sheep) Together with Remarks on Important Clinical (Human) Problems Bull Johns Hopkins Hosp **18**: 359 1907 (*e*) Welch H Hairlessness and Goiter in Newborn Domestic Animals Bulletin 119 Montana Experiment Station September 1917

tained under controlled basal conditions Moreover, to arrive at an *optimal* iodine requirement, it is necessary to take into account individual activity as well as the varied stress and strain of existence

After consideration of the difference in iodine intake between goitrogenous and nongoitrogenous regions and the amount of iodine estimated as necessary to maintain normal metabolic activity, 2 micrograms daily per kilogram of body weight together with the daily basal requirement of 1 microgram can be reasonably justified as an amount sufficient to account for *basal* needs those of ordinary activities and also some for reserve The *optimal* daily requirement would thus be somewhere near 200 micrograms for an adult of 70 Kg, a value compatible with Elmer's deduction from various investigations that the human optimal requirement ranges between 100 and 200 micrograms daily [18] The pregnant woman should receive additional iodine [41a] A sufficient amount will be supplied by the use of iodized salt [39]

Various methods of supplying supplemental iodine to the inhabitants of iodine deficient areas have been advanced These include the use of foods known to be rich in iodine iodinization of water supplies, administration of iodine at regular intervals in the form of solutions or tablets the general use of iodized salt and the consumption of iodized milk

The use of iodized salt has thus far proved the most widely adopted method The nearly universal employment of common salt for seasoning and cooking, as well as the ready preparation and low cost of iodized salt, makes this the popular method The use of milk with an increased iodine content has also been suggested as suitable (fig 1) [8b] especially for children who ordinarily consume large quantities Effective iodine prophylaxis should conform to local conditions, since no single method will reach all those persons who need iodine

The iodized salt originally recommended in 1924 by the Michigan State Medical Society in conjunction with the State Board of Health and subsequently employed in Michigan with such outstanding results originally contained 0 02 per cent of sodium iodide However after careful consideration the Goiter Study Committee of the American Public Health Association reached the conclusion that the addition of 0 01 per cent of potas-

sequently developed by Thompson[61] Plummer and Boothby observed that the daily rate of thyroxine decay ranged between 200 and 400 micrograms Thus, a daily supply of thyroxine in this quantity maintained a normal basal metabolic rate in a totally myxedematous patient Thompson and his group concluded that from 300 to 400 micrograms of thyroxine was necessary to maintain a normal basal metabolic rate in myxedematous patients at bed rest On the basis of these results the amount of thyroxine supplied daily to the circulation by the thyroid gland, in order to maintain normal metabolic activity, is equivalent to from 130 to 260 micrograms of iodine The uncertain factor here, however, is that iodine-containing end products of thyroxine decay may be retained and eventually reutilized by the thyroid gland in the further synthesis of thyroid hormone

Studies of *total iodine balance* constitute the third principle which has been employed (figs 1, 2 and 3) The iodine balance represents the daily amount of iodine lost or retained by the body as ascertained by the difference between the amount of iodine intake and excretion Pioneer determinations of iodine balance were accomplished by von Fellenberg, who reported low values and consequently a low daily requirement[42c] The balance studies of Scheffer made in Pecs Hungary revealed that 54 micrograms of daily iodine intake was sufficient to maintain the iodine balance in a normal person[62]

Ohio State University studies were made on normal persons maintained at bed rest on a monotonous diet low in iodine content under controlled hospital conditions (figs 1 2 and 3) In these circumstances the basal human adult iodine requirement was found to range from 44 to 75 micrograms daily and to average 67 micrograms or approximately 1 microgram per kilogram of body weight[63] This average daily requirement is comparable to that determined by Scheffer However, it should be emphasized that it applies to adults main

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61 Thompson W O McLellan L L Thompson P K and Dickie, L F N The Rates of Utilization of Thyroxine and of Desiccated Thyroid in Man The Relation Between the Iodine in Desiccated Thyroid and Thyroxin J Clin Investigation **12**: 235 1933 Thompson W O Thompson P K Taylor S G Nadler, S B and Dickie L F N The Pharmacology of the Thyroid in Man J A M A **104** 972 (March 23) 1935

62 Scheffer L Ueber die Jodbilanz normaler Menschen Biochem Ztschr **259**: 11 1933

63 Flickinger F M The Iodine Requirement of Man Thesis Columbus Ohio, Ohio State University Department of Surgical Research 1941

iodine supplements such as an adequately iodized salt, and with the persistent education of all peoples to the importance of its continued use, we may look forward with sound hope toward a better control of endemic goiter The newer knowledge of the goitrogenic factors present in certain foods, as well as the significance of certain vitamins causes us to await further developments in our knowledge concerning the *utilization* of available iodine Thus, there may be adduced further evidence for the need of a properly *balanced* diet.

It cannot be too frequently repeated that iodine plays an indispensable role in the human organism and an indisputable role in medicine Its prophylactic usage to insure the well being of man and his essential domestic animals deserves continued emphasis Thus the element iodine is to the normal functioning thyroid gland as water to cultivated ground Deprivation of this necessary substance, even to a lesser degree, may produce changes in the entire organism, harmful to the individual and significant to a people A sufficient amount of iodine intake is a biologic necessity

sium iodide plus a stabilizer should be sufficient [4] The importance of a stabilizer was emphasized in view of previous experience that iodine may be lost from iodized salt and thus impart a yellowness and a halogen odor on liberation of elemental iodine

It has been estimated that the average adult ingests about 6 2 Gm of salt daily Calculated on this basis the approximate amount of potassium iodide intake would be 620 micrograms, which is equivalent to about 474 micrograms of iodine This is more than twice the amount we have suggested as optimal and would amply provide a person with a sufficient reserve

SUMMARY AND CONCLUSION

'Wenn man weisz nicht warum, dann gibt man jod kalium

Such was a useful aphorism to the nineteeth century physician perplexed by a discordance which he often recognized, yet unarmed by the necessary facts, at his time still undisclosed His modern prototype when in a quandary may lean heavily upon vitamins hormones, or antibiotics, nevertheless, he knows that there is both a time and place for the iodides Recent polemic discussion is not new It has persisted in varying degrees throughout more than a century of the use and abuse of iodine, and is now in recrudescence owing to the discovery of the antithyroid drugs Notwithstanding, it has led conclusively to the recognition of iodine as a nutritional necessity a specific indication in the prophylaxis of endemic goiter as well as a most valuable therapeutic agent in the management of thyroid disease

Other dietary factors however, which may play some role in the genesis of endemic goiter are receiving increasing attention Some have been shown to be goitrogenic and to contain a compound not unlike thiouracil in character Yet they appear to act by hindering the normal mode of utilization of iodine in the thyroid cell There ensues a resultant diminution in the formation of the high iodine containing thyroid hormone, with subsequent effects upon the anterior pituitary

Nevertheless it appears established that iodine plays a significant role in the prevention of endemic goiter and its sequelae With the increased consumption of

CHAPTER VII

FLUORINE AND OTHER TRACE ELEMENTS IN NUTRITION

F J McCLURE

There have been important developments regarding the effects of fluorine on dental caries which justify the optimistic view that dental caries may be partially controlled by some form of fluoride therapy The direct fluorination of drinking waters of large com munal centers is in process of study as a caries control measure and represents a unique and heretofore unutil ized approach toward a mass preventive in medicine and dentistry The first direct fluorination of com munity water was begun on Jan 28, 1945, in Grand Rapids Mich Other cities now artificially providing 1 0 part per million of fluorine in their drinking water are, Newburgh N Y , Brantford Ontario, Canada, Midland Mich , Sheboygan and Madison, Wis Evanston Ill , Ottawa, Kan , and Marshall Texas No foodstuff in the average American diet can compare with drinking water containing 1 0 part per million or more of fluorine as a source of fluorine in human nutrition but it cannot be said at this time that fluorine is an essential trace element even for purposes of dental health Although it may become a recommended dietary procedure to supplement children's diets with an optimum quantity of fluoride wherever a fluoride drinking water is not available, present evidence does not justify dietary addition of fluorine

Fluorine research has afforded a striking demonstra tion of the relatively narrow margin of physiologic benefit and physiologic toxicity which characterizes many trace elements Optimum effects of fluorine on dental caries thus are associated with 1 0 part per million of fluorine in the drinking water [1] whereas 1 5 parts per million or slightly more fluorine is the

1 Dental Caries and Fluorine American Association for the Advancement of Science 1946.

CHAPTER VII

FLUORINE AND OTHER TRACE ELEMENTS IN NUTRITION

F. J. McCLURE

There have been important developments regarding the effects of fluorine on dental caries which justify the optimistic view that dental caries may be partially controlled by some form of fluoride therapy. The direct fluorination of drinking waters of large communal centers is in process of study as a caries control measure and represents a unique and heretofore unutilized approach toward a mass preventive in medicine and dentistry. The first direct fluorination of community water was begun on Jan. 25, 1945 in Grand Rapids, Mich. Other cities now artificially providing 1.0 part per million of fluorine in their drinking water are Newburgh, N. Y., Brantford, Ontario, Canada, Midland, Mich., Sheboygan and Madison, Wis., Evanston, Ill., Ottawa, Kan., and Marshall, Texas. No foodstuff in the average American diet can compare with drinking water containing 1.0 part per million or more of fluorine as a source of fluorine in human nutrition but it cannot be said at this time that fluorine is an essential trace element even for purposes of dental health. Although it may become a recommended dietary procedure to supplement children's diets with an optimum quantity of fluoride wherever a fluoride drinking water is not available, present evidence does not justify dietary addition of fluorine.

Fluorine research has afforded a striking demonstration of the relatively narrow margin of physiologic benefit and physiologic toxicity which characterizes many trace elements. Optimum effects of fluorine on dental caries thus are associated with 1.0 part per million of fluorine in the drinking water[1] whereas 1.5 parts per million or slightly more fluorine is the

[1] Dental Caries and Fluorine, American Association for the Advancement of Science, 1946.

beginning level of endemic dental fluorosis[2] The dietary conclusion is obvious, therefore that the indiscriminate use of fluoride supplements must be condemned

In addition to fluorine, manganese, cobalt, zinc and boron are discussed in this review, which continues in point of time from a previous review by Shils and McCollum,[3] published in an earlier issue of the Handbook of Nutrition A number of other reviews concerning minerals in nutrition have appeared in recent years[4]

FLUORINE

Fluorine and Dental Caries —The epidemiologic evidence which demonstrated that excessive fluoride in drinking water is the cause of endemic mottled enamel[2] also suggested the fluorine–dental caries relationship now conclusively associated with domestic waters of optimal fluoride content[5] In one of the most important of the epidemiologic fluoride studies intensity of dental caries attack in school populations (12 to 14 year old children) in eight suburban Chicago communities was inversely correlated with 0 0 to 1 8 parts per million of fluorine in the drinking water[6] Outside the United

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2 Fluorine and Dental Health Publication 19 American Association for the Advancement of Science 1942

3 Shils M E and McCollum E V Trace Elements in Nutrition in Handbook of Nutrition Chicago American Medical Association 1943 chap 9

4 Maynard L A and Smith S E Mineral Metabolism in Luck J M Annual Review of Biochemistry Stanford University Calif Annual Reviews Inc 1947 vol 16 p 273 Watson S J and Smith A. M The Trace Elements in Plant and Animal Nutritio Scottish J Agric **25** 203 1946 Sendroy J Mineral Metabolism in Luck J M Annual Review of Biochemistry Stanford University Calif Annual Reviews Inc 1945 vol 14 p 407 Stare F J Hegsted D M and McKibbin, J M Nutrition in Luck J M Annual Review of Biochemistry ibid p 431 Maynard L A and Loosli J K Mineral Metabolism in Luck J M Annual Review of Biochemistry ibid 1943 vol 12 p 251 McCance R A and Widdowson E M Mineral Metabolism in Luck J M Annual Review of Biochemistry ibid 1944 vol 13 p 315 Underwood F J The Significance of Trace Elements in Nutrition Nutrition Abstr & Rev **9** 515 1940 Cox G J A Critique of the Etiology of Dental Caries in Harris R S and Thimann K V Vitamins and Hormones Advances in Research and Applications New York Academic Press Inc 1944 vol 2 p 255 Armstrong W D Biochemical and Nutritional Studies in Relation to the Teeth in Luck J M Annual Review of Biochemistry Stanford University Calif Annual Reviews Inc 194- chap 11 p 441

5 (*a*) Footnote 1 (*b*) Dean H T Epidemiological Studies in the United States in Dental Caries and Fluorine

6 Dean H T Jay P Arnold F A Jr and Elvove E Domestic Water and Dental Caries II A Study of 2 832 White Children Aged Twelve to Fourteen Years of Eight Suburban Chicago Communities including Lactobacillus Acidophilus Studies of 1 761 Children Pub Health Rep **56** 761 1941

States similar confirmatory results have been reported.[7] Figure 1 is a summary graph of the results of the epidemiologic fluoride studies of Dean and his coworkers.[8]

Whereas inhibition of caries has been demonstrated conclusively for 12 to 14 year old children continuously exposed to fluoride waters, only a few studies apply to older persons. Deatherage observed reduced caries in adult male inductees exposed to fluoride waters[9] starting even after their eighth birthday.[10] Weaver[11]

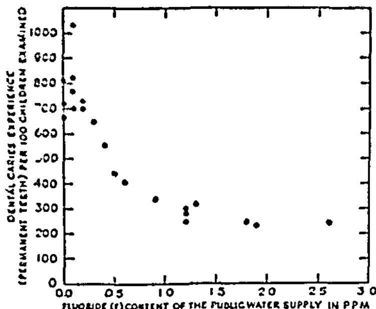


Fig. 1.—Relation between the amount of dental caries (permanent teeth) observed in 7,257 selected 12 to 14 year old white school children of twenty-one cities of four states and the fluoride (F) content of public water supply.

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7. Weaver, R.: Epidemiological Studies in the British Isles and India in Dental Caries and Fluorine.[38] Ockerse, T.: Fluorine and Dental Caries in South Africa in Dental Caries and Fluorine.[38] Shourie, K. L.: Fluorine and Dental Caries in India, Indian J. M. Research 34:97, 1946.

8. Dean, H. T.; Arnold, F. A., Jr., and Elvove, E.: Domestic Water and Dental Caries; V. Additional Studies of the Relation of Fluoride Domestic Waters to Dental Caries Experience in 4,425 White Children Aged Twelve to Fourteen Years, of Thirteen Cities in Four States, Pub. Health Rep. 57:1155, 1942.

9. Deatherage, C. F.: A Study of Fluoride Domestic Waters and Dental Caries Experience in 2,026 White Illinois Selective Service Men, J. Dent. Research 22:129, 1943.

10. Deatherage, C. F.: Study of Fluoride-Containing Domestic Waters and Dental Caries Experience in Two Hundred and Sixty-Three White Illinois Selective Servicemen Living in Fluoride Areas Following the Period of Calcification of the Permanent Teeth, J. Dent. Research 22:173, 1943.

11. Weaver, R.: Fluorosis and Dental Caries on Tyneside, Brit. Dent. J. 76:29, 1944.

extended his observations in England to older persons and studied effects of time of initial fluoride exposure on caries attack He suggested that "fluorine is a caries postponing rather than a caries preventing factor,"[12] a suggestion which does not discredit the significance of fluoride waters for caries control in younger persons A recent report by McKay[12a] is contrary to Weaver,[12] and suggests that resistance to caries, as produced by exposure to fluoride drinking waters, continues into adult life Both of these reports are based on small numbers of individuals They permit no conclusions in these regards and mostly emphasize the uncertainties surrounding the mechanism and the duration of the fluoride anti caries effects

Experimental results give consistent support to the human caries–fluoride relation, i e (*a*) induced experimental caries in small animals is fluoride inhibited,[13] (*b*) dental tissues contain fluorine which may be classified as primary fluorine acquired during growth and calcification of the teeth[14] secondary fluorine acquired after tooth eruption[15] and adsorbed secondary enamel fluorine[16] acquired possibly by local oral enamel sur

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12 Weaver R Fluorine and Dental Caries Further Investigations on Tyneside and in Sunderland Brit Dent J **77** 185 1944

12a. McKay F S Mass Control of Dental Caries Through the Use of Domestic Water Supplies Containing Fluorine Am J Pub Health **38** 828 832 1948

13 (*a*) Hodge H C. and Sognnaes R. F Experimental Caries and a Discussion of the Mechanism of Caries Inhibition by Fluoride in Dental Caries and Fluorine[45] (*b*) Miller B F Inhibition of Experimental Dental Caries in the Rat by Fluoride and Iodoacetic Acid Proc. Soc Exper Biol & Med. **39** 389 1938 (*c*) McClure F J Observations on Induced Caries in Rats III Effect of Fluoride on Rat Caries and on Composition of Rats Teeth J Nutrition **22** 391 1941 (*d*) Shaw J H Schweigert, B S Phillips P H and Elvehjem C A Dental Caries in the Cotton Rat IV Inhibitory Effect of Fluorine Additions to the Diet Proc Soc Exper Biol & Med **59** 89 1945 (*e*) Dale P P and Keyes P H Inhibition of Experimental Dental Caries in Syrian Hamsters by Fluorine and Iodoacetic Acid J Dent Research **24** 194 1945

14 Cox G J Matuschak M C Dixon S F Dodds M L. and Walker W E Experimental Dental Caries IV Fluorine and Its Relation to Dental Caries J Dent Research **18** 481 1939

15 Perry M W and Armstrong W D On the Manner of Acquisition of Fluorine by Mature Teeth J Nutrition **21** 35 1941 McClure F J Fluorine Acquired by Mature Dog s Teeth Science **95** 256 1942 Observations on Induced Caries in Rats IV Inhibiting Effect of Fluoride Ingested Post Eruptively and Prior to the Caries Producing Diet J Dent Research **22** 37 1943

16 Volker J F Hodge H C Wilson H J and Van Voorhis S N The Adsorption of Fluorides by Enamel Dentin Bone and Hydroxyapatite as Shown by the Radio-Active Isotope J Biol. Chem. **134** 543 1940 Norvold R W Inglis J H and Armstrong W D External Acquisition of Fluorine by Enamel J Dent Research **20**: 232 1941 Falkenheim M and Hodge H C A Note on the Mechanism of Fluoride Fixation ibid **26**: 241 1947

face adsorption, (c) reduced solubility [17] and surface charges in enamel [18] and dentin [19] are attributed to fluoride reactions on dental tissues in vitro, (d) fluoride may affect oral bacterial activity [20] and exert antienzymatic effects possibly involved in causation of dental caries [11b] and (e) the ameloblasts (enamel forming cells) are extremely sensitive to fluorine [21]

Perhaps the simplest explanation of the fluorine anticaries action would point to fluorine in dental tissues Limited analytic data reported by Armstrong and Brekhus [22] support the view that enamel of carious teeth contains less fluorine than enamel of sound teeth. The enamel but not the dentin showed this suggestive fluorine difference A more comprehensive survey by McClure [23] refutes this idea as applied to individual teeth. Analyses of dentin and enamel of several hundred sound and carious teeth showing no signs of fluorosis and representing nearly 100 individuals did not reveal differences in fluorine content The enamel of sound and carious teeth contained 0 0102 ± 0 0004 per cent and 0 0098 ± 0 0003 per cent fluorine respectively and dentin from sound teeth contained 0 0241 ± 0 0010 per cent fluorine and from carious teeth 0 0225 ± 0 0007 per cent fluorine Teeth of different types (incisors molars etc) did not differ in fluorine con

17 Hodge and Sognnaes [11b] Volker J F Effect of Fluorine on the Solubility of Enamel and Dentin Proc Soc Exper Biol & Med 42:725 1939 Bibby B G Effectiveness of Various Fluoride Preparations in Reducing Tooth Solubility J Dent Research 23:302 1944 Buonocore, M G and Bibby B G The Effects of Various Ions on Enamel Solubility ibid 24:103 1945 Rae J J and Clegg C T The Effect of Sodium Fluoride on the Solubility of Calcium Phosphate Tooth Enamel and Whole Teeth in Lactic Acid, ibid 24:235 1945 Muhler J C, and Van Huysen G Solubility of Enamel Protected by Sodium Fluoride and Other Compounds, ibid 26:119 1947 Van Huysen G and Muhler J C Enamel Solubility Reducing Effect of Flavored Low Concentration Stannous Fluoride Solution ibid 27:46, 1948

18 Gerould, C H Electron Microscope Study of the Mechanism of Fluorine Deposition in Teeth J Dent Research 24:223 1945 Scott D B, and Wyckoff R. W G Shadowed Replicas of Tooth Surfaces, Pub. Health Rep 61:1397 1946 Restarski J S Gortner R A Jr., and McCay C M Effect of Acid Beverages Containing Fluorides upon the Teeth of Rats and Puppies J Am Dent A 32:668 1945

19 Saunders, W and Schoonover I C Experimental Remineralization of Dentin J Am Dent A 31:1579 1944

20 Harrison R. W Bacterial Flora in Experimental Dental Caries of the Rat, Proc Soc Exper Biol & Med 38:459 1938 Bibby, B G and Van Kesteren M Effect of Fluoride on Mouth Bacteria J Dent. Research 19:591 1940

21 Schour I and Smith M C The Histologic Changes in Enamel and Dentin of the Rat Incisor in Acute and Chronic Experimental Fluorosis Technical Bulletin 52, University of Arizona 1934

22 Armstrong W D and Brekhus P J Possible Relationship Between the Fluorine Content of Enamel and Resistance to Dental Caries J Dent Research 17:393 1938

23 McClure, F J Fluorine in Dentin and Enamel of Sound and Carious Teeth, J Dent. Research, to be published

tent It was suggested that an increase of fluorine in the entire dentition may account for an over all reduction in dental caries experience but that the individual carious teeth in a dentition cannot be expected to show consistently less fluorine in the enamel (or dentin) than do the sound teeth

There are analytic data to show that mottled teeth do contain more than normal quantities of fluorine[24] and fluorine in rats incisor teeth also correlates closely with characteristic striations caused by fluorine in the diet[25]

Variations in fluorine content per se of dental tissues, in many respects would seem destined to affect their physical structure and biochemical properties in vivo in conformity with the in vitro experimental evidence cited The remarkable caries preventive results obtained by topical application of fluoride[6] suggest a change in enamel surface in vivo, due possibly to acquisition of additional enamel fluorine, via surface adsorption Analytic procedure thus far has failed however, to demonstrate any increased fluorine in topically treated teeth[7]

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24 Boissevain C H and Drea, W F Spectroscopic Determination of Fluorine in Bones and Teeth and Other Organs in Relation to Fluorine in Drinking Water J Dent Research **13**: 495 1933 Bowes J H and Murray M M A Chemical Study of Mottled Teeth from Maldon Essex Brit Dent. J **6** 556 1936 Armstrong W D and Breckhus P J Chemical Composition of Enamel and Dentin II Fluorine Content, J Dent Research **17** 25 1938

25 McClure F J Fluorides in Food and Drinking Water A Comparison of Effects of Water Ingested Versus Food Ingested Sodium Fluoride National Institute of Health Bulletin 172 United States Treasury Department Public Health Service 1939

26 (*a*) Cheyne V G Human Dental Caries and Topically Applied Fluorine A Preliminary Report, J Am Dent A **29** 804 1942 (*b*) Bibby B G The Effects of Sodium Fluoride Applications on Dental Caries J Dent Research **22** 07 1943 (*c*) Knutson J W and Armstrong W D The Effect of Topically Applied Sodium Fluoride on Dental Caries Experience I Report of Findings for the First Study Year Pub Health Rep **58** 1701 1943 (*d*) II Report of Findings for the Second Study Year ibid **60** 1085 1945 (*e*) III Report of Findings for the Third Study Year ibid **61** 1683 1946 (*f*) Jordan W A. Wood O B Allison J A and Irwin V D The Effects of Various Numbers of Topical Applications of Sodium Fluoride J Am Dent. A. **33** 1385 1946 (*g*) Knutson J W Armstrong W D and Feldman F M The Effect of Topically Applied Sodium Fluoride on Dental Caries Experience IV Report of Findings with Two, Four and Six Applications Pub Health Rep **62** 425 1947 (*h*) Galagan D J and Knutson J W The Effect of Topically Applied Fluorides on Dental Caries Experience V Report of Findings with Two Four and Six Applications of Sodium Fluoride and Lead Fluoride ibid **62** 1477 1947 (*i*) Bibby B G and Turesky S S A Note on the Duration of Caries Inhibition Produced by Fluoride Applications J Dent. Research **26** 105 1947

27 Armstrong W D and Knutson J W Increment of Fluorine Content of Enamel Following Topical Application of Fluorides to Teeth, J Dent. Research **24** 192 1945

When the causation of caries is discussed the question of enamel solubility usually arises and numerous investigators look to fluorine to so alter enamel and dentin solubility that acid decalcification by bacterial activity will be remarkably retarded. Here again the explanation may be overly simplified when the question is raised as to what quantity of fluorine in the teeth may be protective and at the same time have a significant solubility reducing effect.

Because fluorine is a powerful antienzymatic agent [28] it is suggested that fluorine in the teeth acts antienzymatically. There is little or no evidence in vivo to support this idea. The effect of fluorine on salivary amylase seems inconsequential [29] and fluorine in saliva is not correlated with ingestion of fluorine [30].

Dental Caries and Fluoride Medication.—In the present state of our knowledge the primary objective in fluoride preventive dentistry is to incorporate optimum quantities of fluorine into dental tissues by the most effective, efficient and lasting means which can be devised. Thus experimental fluorination of communal drinking water is an attempt to duplicate mass population exposure to natural fluoride waters and thereby incorporate possibly an optimal quantity of fluorine in developing teeth. Results from these experiments will not be forthcoming for several years although bacteriologic results of somewhat uncertain value have already been published [31].

The beneficial as well as negative results attending the topical application of solutions of sodium fluoride and other fluorides are summarized in the table. While use of fluoride topically seems extremely promising, variations in the procedure, in the solutions used, etc. need to be studied [26b].

McClure [32] estimated the milligram quantities of fluorine ingested via drinking waters containing 1.00 part

28. Borel, H. Inhibition of Cellular Oxidation by Fluorine. Uppsala, 1945.
29. McClure, F. J. Effect of Fluorides on Salivary Amylase. Pub. Health Rep. 54:2165, 1939.
30. (a) McClure, F. J. Domestic Water and Dental Caries. III. Fluorine in Human Saliva. Am. J. Dis. Child. 62:512 (Sept.) 1941. (b) McClure, F. J., Mitchell, H. H., Hamilton, T. S., and Kinser, C. A. Balances of Fluorine Ingested from Various Sources in Food and Water by Five Young Men. J. Indust. Hyg. & Toxicol. 27:159, 1945.
31. Finn, S. B., and Ast, D. B. Lactobacillus Acidophilus Counts in the Saliva of Children Drinking Artificially Fluorinated and Fluorine Free Communal Waters. Science 106:292, 1947.
32. McClure, F. J. Ingestion of Fluoride and Dental Caries. Quantitative Relations Based on Food and Water Requirements of Children One to Twelve Years Old. Am. J. Dis. Child. 66:362 (Oct.) 1943.

per million of fluorine and suggested that the direct addition of about 1 0 mg of fluorine as sodium fluoride daily to children's diets during the first eight years of life be considered as a caries-preventive measure. A dietary supplement of fluoride seems to have possibilities in caries control, but care should be exercised in the use of fluoride tablets Their use is contraindicated where the drinking water contains 0 5 to 1 0 part per million or more of fluorine

A great number of fluoride-containing tablets for daily consumption in lieu of a fluoride drinking water have appeared on the market. The value of these tablets has had no satisfactory demonstration, although several attempts in this direction have been made[33] Most of these tablets contain calcium fluoride or bone meal and some provide vitamins whereas there is no evidence that calcium phosphorus or any of the vitamins enhance the fluorine caries preventive effect.

The idea is erroneous that edible foods grown in areas where fluorine in the local water is above normal are high in fluorine content Analytic data and fluoride fertilization studies[34] and the fact that the majority of fluoride-bearing waters are not surface waters but come from deep wells[b] all contradict this erroneous idea *The tea leaf and certain sea foods*[5] *are exceptionally* high in fluorine but in general no raw foods can be implicated in the causation of fluorosis or in the fluoride prevention of dental caries[35] Small increments of fluorine may be added to certain foods when they are cooked in fluoride waters[36]

Any increase of fluorine in cows milk due to extra fluorine in the cows ration or drinking water is not

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33 Strean, L. P and Beaudet, J P Inhibition of Dental Caries by Ingestion of Fluoride Vitamin Tablets, New York State J Med. **45** 2183 1945 Harootian, S G Influence of Administration of Bone Flour on Dental Caries J Am. Dent. A. **30** 1396 1943

34 Robinson, W O and Edgington G Fluorine in Soils, Soil Sc. **61** 341 1946. Hart, E. B Phillips P H., and Bohstedt, G Relation of Soil Fertilization with Super Phosphates to Fluorine Content of Plants and Drainage Waters, Am J Pub Health **24** 936 1934 MacIntire, W H Winterberg S H Thompson, J G and Hatcher B W Fluorine Content of Plants Fertilized with Phosphates and Slags Carrying Fluorides, Indust. & Engin. Chem. (Indust Ed.) **34** 1469 1942. Churchill, H V Rowley R. J., and Martin, L. N Fluorine Content of Certain Vegetation *in a Western Pennsylvania Area, Analyt. Chem.* **20** 69 1948

35 McClure, F J Low Dental Caries Experience and Food Products in Deaf Smith County Texas, J Am. Dent. A. **31** 1091 1944

36. Smith H. V Smith, M C. and Vavich M. Fluorin in Milk, Plant Foods, and Foods Cooked in Fluorine-Containing Water Mimeographed Report 77 Arizona Agricultural Experiment Station, 1945

to be expected contrary to some such suggestions[37] All the evidence reveals no elevation of fluorine in cows milk due to additional fluorine in the ration or drinking water[38] It should be emphasized certain industrial exposures being disregarded that water borne fluorine is the major fluorine exposure associated with human population groups.

Effects of Fluoride Domestic Waters—When it became evident that 0 5 to 1 0 part per million of fluorine in drinking water did not cause mottled enamel[34] direct fluorination of public water supplies as a caries preventive measure was contemplated although certain health hazards which might arise from this public practice were not to be ignored

Clinical epidemiologic and experimental evidence[34c] suggested a hazard of accumulative toxic fluorosis particularly if a high percentage of the water borne fluorine was retained in the body Particularly incriminating are the reports from fluoride areas outside the United States which suggest toxic effects of excessive quantities of fluoride in drinking waters combined with fluoride contaminated food A discussion of these reports has been presented elsewhere[34c] In brief the consensus is that the fluoride exposure of the afflicted (fluorosed) native people exceeds any level of fluoride encountered in the United States or that other local factors and lack of adequate control data throw doubt on the results reported[39]

In an attempt to assess the hazard of cumulative fluorosis from fluoride waters, an extensive survey of the fluorine concentration of urine specimens of high school boys and of young selectees of the armed forces of the United States was made by McClure and

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37 McClendon J F and Foster W C Concentric Zones of Distribution of Fluorine in Milk and Dental Caries, Federation Proc. 5:67 1946

38 (a) Phillips, P H Hart, E B and Bohstedt G Influence of Fluorine Ingestion upon the Nutritional Qualities of Milk J Biol Chem. 105:123, 1934 (b) Smith M C Varich M and Smith H V Fluorine Content of Milk as Affected by the Amount of Fluorine in the Drinking Water of the Cow *J Dent Research* 20: 86 1941 (c) McClure F J Nondental Physiological Effects of Trace Quantities of Fluorine in Dental Caries and Fluorine.[34a]

39 Kemp, F H Murray M M, and Wilson D C Spondylitis Deformans in Relation to Fluorine and General Nutrition Lancet 2:93 1942 Spira L. Endemic Fluorosis in Great Britain Edinburgh M J 50:237 1943 Khan Y M and Wig, K L Chronic Endemic Fluorosis (with Bone Affections) in the Punjab Indian M Gaz. 80:429 1945

Kinser[40] The data indicate that upward of 90 per cent of water-borne fluorine (in concentrations of 0 5 to 4 5 parts per million of fluorine) is eliminated in the daily urine of teen age boys and young men The results of this fluorine excretion study are shown in figure 2

Fluorine balance studies[41] furnish additional evidence that the adult human body eliminates the major portion of food and water borne fluorine when the quantities

Effects of Topical Applications of Fluorides

Number of Subjects	Age Range	Treatment: Solution	Treatment: Applications	Length of Study	Reduction in Caries Incidence Percentage	Ref No
90	10-13	0 1% NaF	3	1st yr	46	84[b]
39			0	2d yr	30	84[b]
27	4½ 6	0 05% KF	2	<1	50	84
289	7 15	2 0% NaF	7 15	1st yr	40	84
(270)				2d yr	47	84[d]
(242)				3d yr	22	84
472	7 15	2 0% NaF	2	1 yr	9	84[g]
504	7 15	2 0% NaF	4	1 yr	20	84[g]
482	7 15	2 0% NaF	6	1 yr	21	84[g]
94†	1 22†	1 0% NaF †	1†	1 yr †	0†	
241	6-12	2 0% NaF	1	1 yr	5	84[f]
575	6 12	2.0% NaF	2	1 yr	10	84[f]
161	6-12	2 0% NaF	3	1 yr	?1	84[f]
301	7 15	2 0% NaF	2	1 yr	22	84[h]
247	7 15	2 0% NaF	4	1 yr	41	84[h]
?59	7 15	2 0% NaF	6	1 yr	41	84[h]
272	7 15	0 064% PbF_2	2	1 yr	6	84[h]
214	7 15	0 064% PbF_2	4	1 yr	2	84[h]
6	7 15	0 064% PbF_2	6	1 yr	1	84[h]

Acidified to p 4 5

† Arnold F A Jr Dean H T and Singleton D E The Effect on Car es Incidenc of a S ngle Topical Appl at on of a Fluoride Solution to the Teeth of Young Adult Males of a M l tary Population J Dent Research 23 155 1944

ingested do not exceed 4 0 to 5 0 mg of fluorine daily According to these experiments[42] body sweat may contain appreciable quantities of fluorine which may be related to the fluorine being ingested[30b] McClure also found negative effects of water containing 0 5 to 4 5

40 McClure F J and K nser C A Fluo ide Dome t c Waters and Systemic Effects *II Fluo ne Cont nt of U ine in R lation to Fluor ne in Drinking Water* Pub Health Rep 59 1575 1944

41 (a) McClure[a b] Mach e W (b) Scott, E Largent E J Th Absorpt on and Exc etion of Fluo de I The No mal Fluor de Balance J Indust Hyg & Tox col 24 199 194_ (c) Machle W and Larg nt E J The Absorption and Excr tion of Fluo ide *II The M t bol m* at High Levels of Intake ib d 25 112 1943

42 McClure[30b] Mach e Scott and Largent[41b]

parts per million of fluorine on age height weight-relations and bone fracture histories of high school boys and young inductees[43] Although further studies of population groups exposed to fluoride waters are undoubtedly desirable, it seems unlikely that prolonged ingestion of fluorine via a domestic drinking water containing 1 0 to 1.5 parts per million of fluorine, or perhaps more, presents a public health hazard

Fluorine Physiologic Effects and Requirement—According to Lawrenz[44] the growing rat requires less

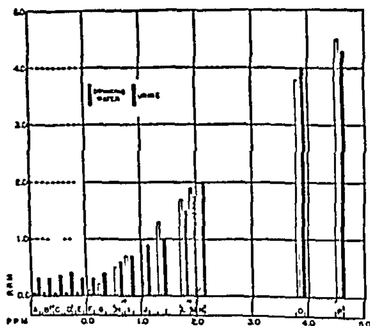


Fig 2—Relation of fluorine in drinking water to fluorine content of urine *A* New Hampshire, *B* Chicago *C*, Washington D C *D*, Waukegan Ill *E* Litl Rock Ark *F* Quincy Ill *G* Indianapolis *H* Oklahoma City *I*, Elgin Ill *J* Aurora, Ill. *K* Joliet Ill *L* Monmouth, Ill *M* Galesburg, Ill. *N* Lubbock Glider Field *O* Lubbock, Texas, and *P* Amarillo, Texas.

than 27 micrograms of fluorine per kilogram which agrees with previous evidence[45] that fluorine probably

43 McClure, F J Fluoride Domestic Waters and Systemic Effects II Relation to Bone Fracture Experience Height and Weight of High School Boys and Young Selectees of the Armed Forces of the United States, Pub Health Rep 60:1543 1944

44 Mitchell H H and Edman M Fluorine in Soils Plants and Animals Soil Sc 60:81 1945

45 Sharpless G R and McCollum, E V Is Fluorine and Indispensable Element in the Diet? J Nutrition 6:163 1933 Evans R J and Phillips P H A New Low Fluorine Diet and Its Effect upon the Rat J Nutrition 18:353 1939

has no essential function in the rat Our present knowl edge also does not permit classification of fluorine as an essential element in human nutrition even as regards dental health The presence of fluorine in dental tissues or in other body tissues is not evidence that fluorine is essential

The metabolism of fluorine by the rat was the subject of extensive study by Lawrenz and Mitchell, and Lawrenz, Mitchell and Ruth Their conclusions are based largely on balance studies and are summarized elsewhere [44]

It is generally difficult to apply animal experimental fluoride results to fluorine exposure via domestic fluoride waters, because of the disproportionate quantities of fluorine involved variations in species susceptibility and duration of exposure Fluorine ingestion from domestic waters even in areas of greatest water fluorine concen tration,[46] would rarely exceed 8 to 10 mg daily (i e less than 0 10 mg per kilogram in the average adult) whereas animal experimental diets usually provide 5 0 mg or more fluorine per kilogram [47] In a recent study, growth serum calcium and phosphorus, hemoglobin and blood coagulation time were not altered by feeding 5 mg fluorine per kilogram, in some instances as long as one year, to 21 litters of dogs involving 99 dogs [47c] A reduction in blood hemoglobin in rats receiving 50 parts per million of fluorine as sodium fluoride in their drinking water was reported by Ginn and Volker [48] but was not confirmed in a subsequent study by McClure and Kornberg [49]

The effects of fluorine on enzymic processes were recently reviewed thoroughly by Borei in connection with the report of his extensive studies on the inhibition by fluoride of oxidative processes in the cell [8]

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46 Fluorine and Dental Health Publication 19 American Medical Association for the Advancement of Science 1942

47 (*a*) Largent E J Machle W and Ferneau, I F Fluoride Ingestion and Bone Changes in Experimental Animals J Indust. Hyg & Toxicol 25 396 1943 (*b*) Bauer W H Bone Changes in Experimental Chronic Fluorine Intoxication J Dent Research 22: 213 1943 (*c*) Greenwood D A Blayney, J R, Skinsnes O K and Hodges P C Comparative Studies of the Feeding of Fluorides as They Occur in Purified Bone Meal Powder Defluorinated Phosphates and Sodium Fluoride in Dogs ibid 25: 311 1946

48 Ginn J T, and Volker J F Effect of Cadmium and Fluorine on the Rat Dentition Proc Soc. Exper Biol & Med 57: 189 1944

49 McClure F J and Kornberg A Blood Hemoglobin and Hematocrit Results on Rats Ingesting Sodium Fluoride J Pharmacol. & Exper Therap 89: 77 1947

MANGANESE

Effects of Manganese Deficiency —There is consistent evidence regarding manganese deficiency to the effect that (*a*) rats and mice react similarly, (*b*) there is a congenital debility in the young, (*c*) manganese is essential for growth in rats and mice (*d*) there is testicular atrophy and sterility (*e*) there is decrease in arginase activity in vitro (*f*) poor bone formation and bone changes in manganese-deficient rats and chicks are similar (*g*) chicks and rats seem to show a similar need for manganese for normal functioning of the nervous system and (*h*) there are lowered hemoglobin concentration and interference with blood regeneration[50] Lameness in pigs and more especially perosis in chicks are well established effects of manganese deficiency[50b]

Disagreement was evident among the observations regarding the reproductive ability of female rats and the viability of their young[50a] and Shils and McCollum[50a] suggested the possibility of three distinct stages of manganese deficiency in the female i e (*a*) viable but defective young are born (*b*) young are born but die shortly and (*c*) a disturbed estrus cycle produces sterility

Wachtel Elvehjem and Hart[50c] in a paired controlled feeding experiment as well as via ad libitum feeding in rats produced additional evidence of (*a*) impaired growth (*b*) less ash in bone (*c*) a slight progressive anemia and (*d*) decreased hemoglobin regeneration They found also a two to three fold increase in blood serum phosphatase activity and no significant change in bone phosphatases Amdur Norris and Heuser[51] from a more recent also controlled feeding experiment reported a small but significant reduction in the alkaline phosphatase in bones of manganese deficient rats Both chicks[52] and rabbits[53] on manganese-defi-

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50 (*a*) Shils M E. and McCollum, E. V Further Studies on the Symptoms of Manganese-Deficiency in the Rat and Mouse J Nutrition **26**:1 1943 (*b*) The Trace Elements in Nutrition in Handbook of Nutrition Chicago, American Medical Association 1943 ch p 9 (*c*) Wachtel, L. W Elvehjem, C. A and Hart E. B Studies on the Physiology of Manganese in the Rat Am J Physiol **140**:7 1943

51 Amdur M O, Norris, L. C and Heuser G F The Need for Manganese in Bone Development by the Rat, Proc. Soc. Exper Biol & Med **60**:254 1945

52 Combs, G F Norris L. C and Heuser, G F The Interrelationship of Manganese Phosphatase and Vitamin D in Bone Development J Nutrition **23**:131 1942 Wiese A C. Johnson B C, Elvehjem C A. Hart, E B and Halpin J G A Study of Blood and Bone Phosphatase in Chick Perosis J Biol Chem **127** 411 1939

53 Ellis, C H Smith S E. and Gates E. M Further Studies of Manganese Deficiency in the Rabbit, J Nutrition **34**:21 1947

has no essential function in the rat Our present knowledge also does not permit classification of fluorine as an essential element in human nutrition even as regards dental health The presence of fluorine in dental tissues or in other body tissues is not evidence that fluorine is essential

The metabolism of fluorine by the rat was the subject of extensive study by Lawrenz and Mitchell, and Lawrenz, Mitchell and Ruth Their conclusions are based largely on balance studies and are summarized elsewhere [44]

It is generally difficult to apply animal experimental fluoride results to fluorine exposure via domestic fluoride waters, because of the disproportionate quantities of fluorine involved, variations in species susceptibility and duration of exposure Fluorine ingestion from domestic waters even in areas of greatest water fluorine concentration [46] would rarely exceed 8 to 10 mg daily (i e, less than 0 10 mg per kilogram in the average adult) whereas animal experimental diets usually provide 5 0 mg or more fluorine per kilogram [47] In a recent study, growth serum calcium and phosphorus, hemoglobin and blood coagulation time were not altered by feeding 5 mg fluorine per kilogram in some instances as long as one year, to 21 litters of dogs involving 99 dogs [47c] A reduction in blood hemoglobin in rats receiving 50 parts per million of fluorine as sodium fluoride in their drinking water was reported by Ginn and Volker [48] but was not confirmed in a subsequent study by McClure and Kornberg [49]

The effects of fluorine on enzymic processes were recently reviewed thoroughly by Borei in connection with the report of his extensive studies on the inhibition by fluoride of oxidative processes in the cell [8]

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46 Fluorine and Dental Health Publication 19 American Medical Association for the Advancement of Science 1942

47 (*a*) Largent E J Machle W and Ferneau I F Fluoride Ingestion and Bone Changes in Experimental Animals J Indust. Hyg & Toxicol **25** 396 1943 (*b*) Bauer W H Bone Changes in Experimental Chronic Fluorine Intoxication J Dent Research **22**: 213 1943 (*c*) Greenwood D A Blayney J R Skinnes O K and Hodges P C Comparative Studies of the Feeding of Fluorides as They Occur in Purified Bone Meal Powder Defluorinated Phosphates and Sodium Fluoride in Dogs ibid **25**: 311 1946

48 Ginn J T, and Volker J F Effect of Cadmium and Fluorine on the Rat Dentition Proc. Soc. Exper Biol & Med **57**: 189 1944

49 McClure F J and Kornberg A Blood Hemoglobin and Hematocrit Results on Rats Ingesting Sodium Fluoride J Pharmacol & Exper Therap **89** 77 1947

MANGANESE

Effects of Manganese Deficiency—There is consistent evidence regarding manganese deficiency to the effect that (*a*) rats and mice react similarly (*b*) there is a congenital debility in the young (*c*) manganese is essential for growth in rats and mice (*d*) there is testicular atrophy and sterility (*e*) there is decrease in arginase activity in vitro (*f*) poor bone formation and bone changes in manganese-deficient rats and chicks are similar (*g*) chicks and rats seem to show a similar need for manganese for normal functioning of the nervous system and (*h*) there are lowered hemoglobin concentration and interference with blood regeneration [50] Lameness in pigs and more especially perosis in chicks are well established effects of manganese deficiency [50b]

Disagreement was evident among the observations regarding the reproductive ability of female rats and the viability of their young [50a] and Shils and McCollum [50a] suggested the possibility of three distinct stages of manganese deficiency in the female i e (*a*) viable but defective young are born (*b*) young are born but die shortly and (*c*) a disturbed estrus cycle produces sterility

Wachtel Elvehjem and Hart [50c] in a paired controlled feeding experiment as well as via ad libitum feeding in rats produced additional evidence of (*a*) impaired growth (*b*) less ash in bone (*c*) a slight progressive anemia and (*d*) decreased hemoglobin regeneration They found also a two to three fold increase in blood serum phosphatase activity and no significant change in bone phosphatases Amdur Norris and Heuser [51] from a more recent also controlled feeding experiment reported a small but significant reduction in the alkaline phosphatase in bones of manganese deficient rats Both chicks [52] and rabbits [53] on manganese defi-

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46 Fluorine and Dental Health Publicat n 19 American Med cal Association for the Advancement of Sc enc 1942

47 (*a*) Largent, E J Machle W and Fern au I F Fluoride Ingestion and Bone Changes n Exper mental Animals J Indust. Hyg & Tox col **25** 396 1943 (*b*) Bauer W H Bone Changes n Expe i mental Ch on c Fluorine Intoxication, J Dent. Research **22** 213 1943 (*c*) Greenwood D A Blayney J R. Skinsn s O K and Hodges P C Comparative Studies of the Feeding of Fluorid s as They Occur in Purified Bone Meal Powder D fluor nated Phosphates and Sodium Fluor de in Dogs ibid **25** 311 1946

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49 McClure F J and Kornberg A Blood Hem glob n and Hematocrit Res lts on Rats Ingesting Sodium Fluor de J Pharmacol & Exper Therap **89** 77 1947

deposition of fat in the liver of rats. An interaction between choline and manganese was indicated by the fact that this lipotropic action of manganese was much greater when the choline content of the diet was lowest. Bone fat as well as liver fat was reduced by both manganese and choline.

The addition of 10 Gm. of manganese to the daily ration of dairy cows changed the manganese content of cows' milk from 21.9 to 61.5 parts per million.[60] This appears to be the only such report of an induced change in the manganese content of milk.

Radiomanganese Studies.—Several studies utilizing radiomanganese have appeared. Two studies with chicks[61] and rats[62] confirm evidence of practically complete elimination of manganese through the feces. In both manganese-deficient and control chicks[61] the major part of orally administered manganese was excreted. Labeled manganese given orally did not appear in bone, indicating that the manganese requirement of bone may be small.[61] Orally ingested manganese is poorly absorbed even in the fasting animal.[62]

As has proved true in regard to many studies on unlabeled manganese in numerous animal species,[63] radiomanganese studies show the liver to be a most active *organ in manganese metabolism.*[64] *From 50 to 75* per cent of the intestinal excretion of labeled manganese was estimated to come from the bile.[62] In the chick the role of manganese in hepatic function cannot be identified with arginase,[65] since chick liver does not contain arginase.

In experiments on the distribution of intravenously administered colloidal sols of manganese dioxide con

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60 Archibald, J. C., and Lindquist, H. G.: Manganese in Cow Milk. J. Dairy Sc. 26: 325, 1943.

61 Mohamed, M. S., and Greenberg, D. M.: A Tracer Study with Mn^{56} on Chicks with Perosis Produced by a Synthetic Manganese Deficient Diet. Proc. Soc. Exper. Biol. & Med. 54: 197, 1943.

62 Greenberg, D. M., Copp, D. H., and Cuthbertson, E. M.: Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes. VII. The Distribution and Excretion, Particularly by Way of Bile, of Iron, Cobalt and Manganese. J. Biol. Chem. 147: 749, 1943.

63 Lorenzen, E. J., and Smith, S. E.: Copper and Manganese Storage in the Rat, Rabbit and Guinea Pig. J. Nutrition 33: 143, 1947.

64 Mohamed and Greenberg.[61] Greenberg, Copp and Cuthbertson. Born, H. J., Timofeeff, H. A., Resonsky and Wolf, I. M.: The Distribution of Manganese in the Animal Organism with Mn^{56} as Indicator. Naturwissenschaften 31: 246, 1943.

65 Sumner, J. B., and Somers, G. F.: Chemistry and Methods of Enzymes, ed. 2. New York, Academic Press, Inc., 1947.

cient diets have shown reduced phosphatase activity In this later rabbit study[53] food intake of control and deficient animals was equalized according to Mitchell's paired feeding technic and a detrimental effect of manganese deficiency on growth and on fresh weight, percentage of ash, total ash, density and length of humerus, was demonstrated

After characteristic symptoms of manganese deficiency in the rabbit had been established, it became possible to determine to some extent the nutrient requirement of the element Thus, Smith and Ellis and others[54] found that rabbits receiving but 0 3 mg of manganese daily had normal bone normal phosphatase activity of bone and normal arginase activity of the liver, but there was the suggestion that this much manganese was not sufficient for normal growth

Physiologic Effects of Manganese—Experiments related to several physiologic effects of manganese have appeared recently The suggestion by Rudra,[55] that manganese played a role in the synthesis of ascorbic acid was not confirmed[56] Skinner and McHargue[57] presented evidence in support of a role of manganese in the synthesis of hemoglobin by showing with rats that manganese combined with iron and copper gave better results than iron and copper alone Skinner and McHargue[57] suggested that manganese may supplement the action of copper This is one of several conflicting reports on the relations of manganese and copper in hemoglobin synthesis[58]

Manganese chloride administered subcutaneously in a single dose to white rats, in dosages greater than 180 mg per kilogram caused an enamel hypoplasia[58b] An interesting observation reported by Amdur Norris and Heuser[59] is that manganese tended to prevent the

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54 Smith S E Ellis G H Lobb D Thompson R M Lorenzen E. J and Larson E J Studies on the Manganese Requirement of Rabbits J Nutrition **34** 33 1947

55 Rudra M N Role of Manganese in the Biological Synthesis of Ascorbic Acid Nature London **153** 743 1944

56 Skinner J T and McHargue J S Experiments to Ascertain the Effect of Manganese on the Synthesis of Ascorbic Acid in the Guinea Pig, Am J Physiol. **145** 566 1946

57 Skinner J T and McHargue J S Supplementary Effect of Arsenic and Manganese on Copper in the Synthesis of Hemoglobin Am J Physiol **145** 500 1946

58. (*a*) Skinner and McHargue (*b*) Wessinger G D and Weinmann J P The Effect of Manganese and Boron Compounds on the Rat Incisor Am J Physiol **139** 233 1943

59 Amdur M O Norris, L. C and Heuser G F Lipotropic Action of Manganese J Biol. Chem **164** 783 1946

of cobalt failed[73] and no deficiency symptoms result in rats[74] or else the requirement is extremely small, i.e., less than 0.003 part per million daily.[74] It has become increasingly evident that cobalt may not act directly on the ruminant host but within the rumen[75] where microorganisms concerned possibly with the synthesis of some of the B vitamins may be affected.[75] In keeping with this idea Ray, Weir, Pope and Phillips[76] have obtained data which indicate a slightly lower concentration of niacin and possibly of the vitamin B_6 group in the blood of cobalt deficient sheep.

Cobalt Metabolism Using Radioactive Cobalt.—When labeled cobalt in trace physiologic quantities is used, results are consistent in indicating, via measurements of body retention and tissue concentration, that the direct requirement of cobalt by ruminants must be small indeed and if required by other animals the quantity is also small.[77]

Orally administered radiocobalt was only poorly absorbed by rats[77] and a large portion appeared in the feces. Excretion of absorbed cobalt was chiefly by way of the urine. The bile is an important excretory path and considerable cobalt was found in the liver which suggested a role of cobalt in liver metabolism.

No significant amounts of injected cobalt reached rumen contents and little rumen ingested cobalt (via

73 Thompson, J. F., and Ellis, G. H.: Is Cobalt a Dietary Essential for the Rabbit? J. Nutrition **34**: 121, 1947.

74 (a) Underwood.[69] (b) Underwood, E. J., and Elvehjem, C. A.: Is Cobalt of Any Significance in the Treatment of Milk Anemia with Iron and Copper? J. Biol. Chem. **124**: 419, 1938. (c) Houk, A. E. H., Thomas, A. W., and Sherman, H. C.: Some Interrelationships of Dietary Iron, Copper and Cobalt in Metabolism. J. Nutrition **31**: 609, 1946.

75 McCance, R. A., and Widdowson, E. M.: Mineral Metabolism, in Luck, J. M.: Annual Review of Biochemistry, Stanford University, Calif., Annual Reviews, Inc., 1944, vol. 13, p. 315.

76 Ray, S. N., Weir, W. C., Pope, A. L., and Phillips, P. H.: The Concentration of Some B Vitamins in the Blood of Normal and Cobalt Deficient Sheep. J. Nutrition **34**: 595, 1947.

77 (a) Greenberg, D. M., Copp, D. H., and Cuthbertson, E. M.: Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes. VII. The Distribution and Excretion, Particularly by Way of the Bile, of Iron, Cobalt and Manganese. J. Biol. Chem. **147**: 749, 1943. (b) Comar, C. L., Davis, G. K., Taylor, R. F., Huffman, C. F., and Ely, R. E.: Cobalt Metabolism Studies. II. Partition of Radioactive Cobalt by a Rumen Fistula Cow. J. Nutrition **32**: 61, 1946. (c) Cobalt Metabolism Studies. III. Excretion and Tissue Distribution of Radioactive Cobalt as Administered to Cattle. Arch. Biochem. **12**: 257, 1947. (d) Sheline, G. E., Chaikoff, I. L., and Montgomery, M. L.: The Elimination of Administered Cobalt in Pancreatic Juice and Bile of the Dog as Measured with Its Radioactive Isotope. Am. J. Physiol. **145**: 285, 1946. (e) Archibald, J. G.: Cobalt in Cows' Milk. J. Dairy Sc. **30**: 293, 1947.

taining about 1 per cent of 310 day manganese, to human beings and dogs, liver manganese in human beings also appeared to be high[66] In the opinion of these workers[66] the pancreas as well as the liver may have special significance in manganese metabolism

Manganese and Enzyme Action — Manganese, although increased twentyfold in the diet of rats, had no effect on the activation of cocarboxylase in vivo as measuured by the concentration of bisulfite binding substances in the blood[67]

Smith[68] studied the mechanism of manganese activation of l leucine aminoexopeptidase and expressed the belief that the action of this metal ion is due to the formation of a true metal protein enzyme compound

The micro determination of manganese has been studied from three different angles, (*a*) microcolorimetric,[69] (*b*) microbiologic[70] and (*c*) a method utilizing the catalytic properties of manganese in an oxidation reaction[71]

COBALT[71a]

Cobalt is required by ruminants but, strangely enough, not by other grazing animals (horses) or other species[72] Attempts to demonstrate a cobalt deficiency in rabbits with a diet containing 0 0024 part per million

66 Sheppard C W Wells F B Hahn P F and Goodell J P B Distribution of Intravenously Administered Colloidal Sols of Manganese Dioxide and Gold in Human Beings and Dogs Using Radioactive Isotopes J Lab & Clin Med **32**: 274, 1947

67 Skinner J T and McHargue J S Effect of Manganese Intake Upon Concentration of Bisulfite Binding Substances in Blood Am J Physiol **141**: 647 1944

68 Smith E Manganese and l Leucine Aminoexopeptidase J Biol Chem **163**: 15 1946

69 Gates L M and Ellis G H A Microcolorimetric Method for the Determination of Manganese in Biological Materials with 4 4 Tetra methyldiaminotriphenylmethane J Biol Chem **168**: 537 1947

70 Bentley O C Small E E and Phillips P H A Microbiological Method for the Determination of Manganese J Biol. Chem **170**: 343 1947

71 Kun E Microdetermination of Manganese in Biological Material by Means of Catalysis J Biol Chem **170**: 509 1947

71a Since completion of this review E L Rickes N C Brink F R Koniuszy T R, Wood and K T Folkers (Science **108**: 134 1948) have reported the presence of cobalt in the new B₁₂ vitamin Inasmuch as this vitamin is identified with remarkable effects in pernicious and other anemias this discovery may explain some of the relations of cobalt to blood chemistry and may likewise extend the requirement of cobalt to other animals as well as ruminants

72 (*a*) Russell F C Minerals in Pasteur Deficiencies and Excesses in Relation to Animal Health Technical Communication 15 Imperial Bureau of Animal Nutrition Scotland 1944 (*b*) Underwood E J The Significance of the Trace Elements in Nutrition Nutrition Abstr & Rev **9**: 515 1940

recently [81] Wintrobe [81g] studied the effect of cobalt on the anemia produced by inflammation induced by injection of turpentine and found it was largely overcome in the rat by cobalt. Cobalt polycythemia was developed in rats regardless of the addition of choline or methionine to the diet but the addition of cystine was distinctly inhibitory [81f]

A role of cobalt in cell metabolism is suggested by its activating effect on arginase [82] Cobalt is also an effective inhibitor of growth and respiration of various micro-organisms animal tissues and tumors. The action of histidine in overcoming this cobalt inhibitory effect is being studied [83]

ZINC

A comprehensive review of zinc emphasizing its toxicity has been presented [84] Prior to this survey [84] it was surmised that use of zinc in war production might have produced unsuspected features of zinc toxicity. No new toxic manifestations were noted, however and the usual precautions in industrial production and use of zinc are still necessary

Interest in a requirement of zinc is stimulated by evidence of the presence of zinc in purified carbonic

81 (a) Dorrance S S Thorn, G W Clinton M Edmonds H W., and Farber S Effect of Cobalt on Work Performance Under Conditions of Anoxia, Am J Physiol **139**: 399 1943 (b) Davis J E. The Effect of Oxygen, Soybean Lecithin, Carbamyl Choline and Furfuryl Trimethyl Ammonium Iodide on Experimental Polycythemia J Pharmacol. & Exper Therap **78**: 37 1943 (c) Warren C O Schubmehl, Q D and Wood J R Studies on the Mechanism of Cobalt Polycythemia Am J Physiol **142**: 173 1944 (d) Orten, J M, and Orten A. U The Production of Polycythemia by Cobalt in Rats Made Anemic by a Diet Low in Protein Am J Physiol. **144**: 464 1945 (e) Stanley A. J Hepp H C. and Hellbaum A A Observations on Cobalt Polycythemia I Studies on the Peripheral Blood of Rats Proc. Soc. Exper Biol & Med **61** 130 1946 (f) Bucciero M C and Orten, J M The Effects of Certain Amino Acids and Choline on the Production of Polycythemia by Cobalt, Federation Proc. **6**: 403 1947 (g) Wintrobe, M M Grinstein M Dubash J J Humphreys, S R Ashenbrucker H and Worth, W The Anemia of Infection VI The Influence of Cobalt on the Anemia Associated with Inflammation Blood **2**: 323 1947

82 Sumner J B and Somers C F Chemistry and Methods of Enzymes, ed. 2 New York, Academic Press Inc. 1947 Anderson A B Activation of Jack Bean Arginase by Cobalt Manganese and Iron, Biochem J **39**: 139 1945

83 Burk D Hearon J Caroline L and Schade A L. Reversible Complexes of Cobalt, Histidine and Oxygen Gas J Biol Chem **165**: 723 1946

84 Hegsted D M McKibbin J M and Drinker C K. The Biological, Hygienic and Medical Properties of Zinc and Zinc Compounds Supplement 179 to the Public Health Reports Federal Security Agency United States Public Health Service 1945

a rumen fistula) reached the blood [77b] Orally admin istered labeled cobalt was 80 per cent eliminated in the feces, 0 5 per cent in urine [77c] Relatively insignificant absorption was indicated by failure to find cobalt in blood milk or saliva Labeled cobalt injected intravenously in dogs did not appear in significant amounts in the pancreatic juice, but a total of 2 0 to 5 0 per cent was eliminated in forty eight and seventy two hours respectively in the bile [77d]

Cobaltous acetate (500 mg daily) in rations of dairy cows increased the cobalt in milk from 0 6 mg up to 2 4 mg [77e] Comar and Davis [78] compared the distribu tion of injected radioactive cobalt in swine rabbits and young calves and found no evidence of species differences Their findings "support the view that the major function of cobalt in the ruminant is a localized action in the rumen but do not exclude the possibility of a hematopoietic function'

The foregoing evidence which implicates the liver as an important depository for radiocobalt is in agree ment with the analytic data of Askew and Watson,[79] which showed that radioinactive cobalt given to deficient sheep accumulated in greatest amount in the liver, with only slight increases in spleen and kidney

Cobalt Polycythemia —An exhaustive review of diet ary factors (vitamins, amino acids and minerals) which are concerned in erythropoiesis has appeared recently [80] Among the minerals involved—iron, copper and cobalt —cobalt is unique, i e a deficiency of cobalt results in anemia, small amounts of cobalt produce erythropoiesis and larger amounts depress erythropoiesis Although symptoms of endemic cobalt diseases are not specific involvement of the erythropoiesis is indicated by the anemia which is generally observed in cobalt deficient animals

Cobalt polycythemia is easily produced in a number of animal species [79] but the mechanism is still unknown A number of reports on this subject have appeared

78 Comar C L and Davis G K Cobalt Metabolism Studies IV Tissue Distribution of Radioactive Cobalt Administered to Rabbits Swine and Young Calves J Biol Chem **170** 379 1947

79 Askew H O and Watson J Correlation of Cobalt Content of Organs of Healthy and Bush Sick Sheep at Glenhope New Zealand New Zealand J Sc & Tech **25** 81 1943

80 Cartwright G E. Dietary Factors Concerned in Erythropoiesis Blood **2**: 111 and 256 1947

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82 Sumner J B and Somers C F Chemistry and Methods of Enzymes ed. 2 New York Academic Press Inc. 1947 Anderson A B Activation of Jack Bean Arginase by Cobalt, Manganese and Iron Biochem. J 39:139 1945

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81 (*a*) Dorrance S S Thorn G W Clinton M Edmonds H W and Farber S Effect of Cobalt on Work Performance Under Conditions of Anoxia Am J Physiol **139**: 399 1943 (*b*) Davis J E The Effect of Oxygen, Soybean Lecithin Carbamyl Choline, and Furfuryl Trimethyl Ammonium Iodide on Experimental Polycythemia J Pharmacol & Exper Therap **79** 37 1943 (*c*) Warren C O Schubmehl Q D and Wood I R Studies on the Mechanism of Cobalt Polycythemia Am J Physiol **142**: 173 1944 (*d*) Orten, J M and Orten A U The Production of Polycythemia by Cobalt in Rats Made Anemic by a Diet Low in Protein Am J Physiol. **144** 464 1945 (*e*) Stanley A J Hopps H C and Hellbaum A A Observations on Cobalt Polycythemia I Studies on the Peripheral Blood of Rats Proc. Soc Exper Biol & Med **61** 130 1946 (*f*) Bucciero M C and Orten J M The Effects of Certain Amino Acids and Choline on the Production of Polycythemia by Cobalt, Federation Proc. **6** 403 1947 (*g*) Wintrobe, M M Grinstein M Dubash J J Humphreys S R. Ashenbrucker H and Worth W The Anemia of Infection VI The Influence of Cobalt on the Anemia Associated with Inflammation, Blood **2**: 323 1947

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83 Burk D Hearon J Caroline L and Schade, A L Reversible Complexes of Cobalt, Histidine and Oxygen Gas J Biol. Chem. **165**: 723 1946

84 Hegsted D M McKibbin J M and Drinker C K The Biological, Hygienic, and Medical Properties of Zinc and Zinc Compounds, Supplement 179 to the Public Health Reports, Federal Security Agency United States Public Health Service 1945

anhydrase[85] Use of radiozinc (Zn ?) has furnished new information on zinc metabolism[86]

A need for zinc by the rat has been known for some time,[87] but it has been more difficult to determine in the mouse[88] However, zinc starvation in mice did produce retarded growth localized alopecia and affected hepatic and renal catalase.[89] A change in hepatic esterase, or concentration of riboflavin in liver and kidneys changes in enamel and dentin and distinctive gross symptoms did not occur in this experiment[89] Food consumption was ad libitum however, and it would be of interest to confirm deficiency effects[89] under conditions of controlled feeding

While a number of experiments suggest that the pancreas is involved in zinc metabolism[90] evidence is contradictory regarding the relations of zinc and insulin[91] In support of the view that the acinar portion of the pancreas may be associated with zinc metabolism

85 Keilin D and Mann T Carbonic Anhydrase, Nature, London **144** 442 1939 Scott, D A and Mendive J R Chemical Observations on Carbonic Anhydrase, J B ol Chem **140** 445 1941 Hove E Elvehjem C A and Hart E B The Relation of Zinc to Carbonic Anhydrase ibid **136** 425 1940

86 (*a*) Montgomery, M L Sheline G E and Chaikoff I L The Elimination of Adm ni tered Zinc in Pancreatic Ju ce Duodenal Juice and Bile of the Dog as Measured by Its Radioactive Isotope (Zn^{65}) J Exper Med. **78** 151 1943 (*b*) Sheline G E Chaikoff I L Jones, H B and Montgomery M L Stud es on the Metabolism of Zinc with the Aid of Its Radioactive Isotope I The Excret on of Admin stered Zinc in Urine and Feces J Biol Chem **147** 409 1943 (*c*) Studies on Metabolism of Zinc with A d of Its Radioactive Isotope Distribution of Administered Radioactive Zinc in Tissues of Mice and Dogs, ibid **149** 139 1943

87 (*a*) Stirn F E. Elvehjem C. A and Hart E. B The Indispensability of Zinc in Nutrition of the Rat J Biol Chem **109** 347 1935 (*b*) Hove E. Elvehjem C A and Hart, E. B The Physiology of Zinc in the Nutrition of the Rat Further Studies on Zinc Deficiency in Rats Am J Phys ol **124**: 750 1938 (*c*) Day H G and McCollum E. V Effects of Acute Dietary Zinc Deficiency in the Rat, Proc. Soc Exper Biol & Med **45**: 82 1940

88 McHargue J S Further Evidence That Small Quantities of Copper Mangane e and Z nc Are Factors in the Metabolism of Animals, Am. J Physiol **77** 245 1926 Hubbell, R B and Mendel L. B Zinc and Normal Nutr tion J Biol. Chem **75** 567 19 7 Bertrand G and Bhattacherjee R C. Recherches sur l action combinée du zinc et des vitamines dans l alimentation des animaux, Bull. Soc. ch m. b ol **17** 1137 1935

89 Day H G and Skidmore, B E Some Effects of D etary Z nc Deficiency in the Mouse J Nutrition **33** 27 1947

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91 Scott D A and Fisher A M The Insulin and the Z nc Content of Normal and D abetic Pancreas J Clin. Inve tigat on **17** 725 1938 Eisenbrand J and Sienz M. Ueber den Zinkgehalt von menschlichen Pankreasdrusen Ztschr f phys ol. Chem. **268** 1 1941

Montgomery, Sheline and Chaikoff[86a] found 11 per cent of administered radiozinc (Zn^{7}) excreted in the pancreatic juice of the dog in fourteen days Maximum excretion in bile was only 0 4 per cent in eight days Radiozinc was found in large amounts in juice obtained from an isolated loop of the duodenum Sheline, Chaikoff *Jones and Montgomery*[86b] *injected minute* quantities of zinc intravenously in dogs and mice and found that by far the largest fraction was eliminated in the feces In dogs and mice the most active turnover of radiozinc was in liver pancreas and pituitary gland The least activity occurred in red blood cells brain, skeletal muscles and skin[86c] The extensive distribution of zinc in the animal body and its presence in important intestinal secretions gain support from these results[86b, c]

Forty-two zinc balances on normal human patients reported by McCance and Widdowson[92] presented a condition also noted for injected radiozinc[86b, c], i e. *practically all food ingested zinc was eliminated in the* feces Normally 0 3 mg zinc daily was excreted in the urine and this quantity did not vary with the intake of zinc by mouth or by injection Patients with albuminuria excreted about seven times the normal amount in urine, although this amount of zinc was not correlated with the degree of albuminuria In contrast with this result[92] Fairhall and Hoyt[93] previously found no relation of zinc to urinary albumin but zinc was *somewhat increased in the urine of uremia and tuber*culosis It would appear that the kidney normally has little or no zinc excretory function and does not vary its excretion in relation to dietary zinc or even when plasma zinc is increased after zinc injection Traces of zinc in the urine as suggested by McCance and Widdowson[9] possibly represent an end product *of some metabolic function of the kidney itself*

Zinc toxicity studies in rats provided Smith and Larson[94] with *evidence of an antagonistic effect of* copper and liver on reduced growth and hemoglobin

92 McCance R. A. and Widdowson, E M The Absorption and Excretion of Zinc, Biochem J 36:69 194–

93 Fairhall L. T and Hoyt L. H The Excretion of Zinc in Health and Disease, J Clin Investigation 7:537 1929

94 Smith, S E., and Larson, E. J Zinc Toxicity in Rats Antagonistic Effects of Copper in Liver J Biol. Chem. 163 29 1946.

levels associated with zinc toxicosis and called further attention to the interrelation and interdependence of mineral elements in physiologic effects

Although important relations to numerous enzyme systems[95] and certain animal experiments[96] suggest a human need for zinc, there is no direct information on this requirement In a report by Stevenson[97] the possibility of a human zinc requirement was remotely suggested by evidence of low carbonic anhydrase activity in the blood of premature infants Wide distribution in plants and animals however, contraindicates a deficiency of zinc occurring in practical animal and human nutrition

BORON

Boron occurs extensively in animal tissues,[98] but no evidence of a boron requirement in animal nutrition has been noted Both oral ingestion of boron and absorption from boric acid applied in the form of an ointment or a saturated solution may cause serious and even fatal cumulative boron poisoning[99]

Teresi Hove Elvehjem and Hart[100] prepared a ration lower in boron than that previously used[101] Although the animals failed to eat the ration properly, it was indicated that a boron intake of 0 6 microgram per rat per day would probably satisfy normal growth

In plant nutrition boron is poorly absorbed from mediums of low potassium content[102] Assuming that a similar relation might exist in animal nutrition, Skinner and McHargue[103] studied the response of rats to boric acid and borax supplements in rations low in potassium Due to extreme potassium deficiency all the animals

95 Hegsted McKibbon and Drinker[89] Footnote 40
96 Hove Elvehjem and Hart[4-b] Day and McCollum[43] Day and Skidmore[44]
97 Stevenson S S Carbonic Anhydrase in Newborn Infants J Clin Investigation **22** 403 1943
98 Yue P S The Biological Distribution of Boron Dissert. Johns Hopkins University 1937
99 Pfeiffer C C Hallman, L F and Gersh I Boric Acid Ointment A Study of Possible Intoxication in the Treatment of Burns J A M A **128**: 266 (May 26) 1945
100 Teresi J D Hove E. Elvehjem C A and Hart E. B Boron in the Nutrition of the Rat Am J Physiol **140** 513 1944
101 Hove E Elvehjem C A and Hart E. B Boron in Animal Nutrition Am J Physiol **127** 689 1939
102 Reeve E and Shive J W Potassium Boron and Calcium Boron Relationships in Plant Nutrition Soil Sc **57** 1 1944
103 Skinner J T and McHargue J S Response of Rats to Boron Supplements when Fed Rations Low in Potassium Am J Physiol **143** 385 1945

grew little, but boron supplements accounted for longer survival periods, and after twenty-one days the rats on boron supplements contained 47 per cent more glycogen in their livers than the controls not given boron supplements Stores of body fat were favored by liberal supplementation" with boron compounds The variable food consumption by rats on the two rations was not considered

In a similar study Follis[104] did not find heart and renal lesions in the rat due to potassium deficiency any different with and without boron supplements and contrary to the results of Skinner and McHargue[103] boron had no effect on growth or survival time

An eleven to sixteen day boric acid regimen (3 Gm daily) was studied in 4 normal adults[105] This much boron was not particularly toxic to these adults as indicated by no effects on basal metabolism or other effects being noted

Excretion of borate by the dairy cow was studied in forty day balances in 2 Ayrshire cows[106] Feeding 16 to 20 Gm borax daily caused the milk concentration of boron to rise from 0 7 to 3 0 parts per million which was not considered a public health hazard[106] No diuretic effects loss in weight or other ill effects occurred A retention of boron in the body was not detectable and boron excretion rapidly returned to normal at the end of experimental feeding

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105 Liljest and G and Nylin G Boric Acid and Standard Metabolism, Acta phys ol Scandinav **5** 194 1943

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CHAPTER VIII

THE VITAMIN B COMPLEX

C. A. ELVEHJEM

The group of dietary factors, the vitamin B complex, is included in the larger class of water-soluble vitamins because like all vitamins, they are required by the body in small amounts and because the individual chemical compounds are soluble in water although the degree of solubility varies from the sparingly soluble riboflavin to the readily soluble choline These are the main characteristics common to the individual vitamins because their functions in the living cell may differ greatly and their chemical structure may vary from the simple configuration of nicotinic acid to the more complex molecular structure of thiamine and riboflavin The vitamin B complex is usually differentiated from the other water-soluble vitamins such as vitamin C and related factors on the basis of the source material used in early isolation work and the kind of experimental animals employed for the assay

No attempt will be made to cover in this short summary the vast amount of literature which is accumulating on the water-soluble vitamins A symposium entitled The Vitamins [1] published by the American Medical Association in 1939 includes a survey of the facts known at that time This chapter is a revised form of chapter 11 in the first Handbook of Nutrition and will include only a general summary of the more significant facts and reference will be made to original papers only when they have been published within the past few years Since this review will stress the nutritional importance of these vitamins the description of the clinical aspects of the deficiency diseases resulting from their deficiency will of necessity be

1 The Vitamins, *Chicago, American Medical Association, 1939*

2. Handbook of Nutrition, Chicago, American Medical Association 1943

limited A recent publication by Jolliffe, Tisdall and Cannon[3] includes a description of the clinical symptoms

The B complex now is known to consist of at least a dozen separate factors ten of which can be obtained in crystalline form Each factor will be discussed separately and in more or less chronologic order of its recognition and identification

THIAMINE

Thiamine hydrochloride is a white crystalline sub stance readily soluble in water, possessing a nutlike and salty taste and a yeastlike odor The empiric formula is $C_{12}H_{18}N_4OSCl_2$, and the compound has the struc tural formula shown in figure 1

It is rapidly destroyed in neutral or alkaline solutions because of hydrolytic cleavage into its constituent pyrimidine and thiazole rings, but in acid solutions it

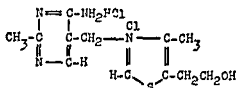


Fig 1 —Structural formula of thiamine hydrochloride

can be sterilized for half an hour at 120 C without appreciable loss of activity In the dry form it is very stable and is not readily destroyed by oxidation Its activity is rapidly destroyed by sulfite a fact which may explain the loss of thiamine during the sulfuring of fruits This vitamin also seems to be very rapidly destroyed in dehydrated meats and vegetables when the moisture content is approximately 5 per cent

In foods and in tissues it occurs both in the free form and as thiamine pyrophosphate or cocarboxylase In the latter form it functions in the living cell as a coenzyme in carbohydrate metabolism especially in the metabolism of alpha keto acids In thiamine deficiency the utilization of carbohydrate is incomplete and pyru vic acid accumulates in the tissues, a condition which is used in determining thiamine insufficiency Many of the symptoms which have been observed in beri beri may be related to faulty carbohydrate metabolism,

3 Jolliffe N Tisdall F F and Cannon, P R Handbook on Clinical Nutrition New York Paul B Hoeber Inc 1950

although it is still difficult to differentiate an uncomplicated thiamine deficiency from multiple deficiencies. Some of the nerve lesions which have been described in experimental animals suffering from polyneuritis are certainly related to a deficiency of riboflavin but there is also good evidence that a lack of thiamine may directly cause neuropathy.

The variety of symptoms seen in human beings has been summarized by Williams and Spies[4] Jolliffe[5] and Jolliffe and his co workers[3] Wilder[6] has pointed out that the type of symptoms produced depends to a considerable extent on the rate at which the deficiency develops, but in all cases the subjects become depressed, irritable quarrelsome uncooperative and fearful. A relationship between thiamine deficiency and cardiac function has been recognized for many years and Blankenhorn and his co workers[7] have recently suggested seven criteria for the diagnosis of "beriberi heart" Anemia of the hyperchromic type has also been described in a number of thiamine deficient patients.

The Food and Nutrition Board of the National Research Council recommends 1 2 to 1 8 mg as the *daily thiamine allowance for the average adult man.* The minimum daily requirement as established by the United States Food and Drug Administration is 1 mg. The requirement is increased in periods of active growth and during pregnancy and lactation. Pathologic conditions such as fevers and hyperthyroidism in which there is a general increased metabolism also increase the requirement. The effect of external temperature *on the thiamine requirement of experimental* animals has been given considerable attention. Mills[8] originally reported that rats need twice as much thiamine per unit of food at 91 F as at 65 F. *However*

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4 Williams R R and Spies, T D Vitamin B_1 (Thiamin) and Its Use in Medicine New York The Macmillan Company 1938

5 Jolliffe N Recent Advances in Clinical Applications of the B Vitamins J Am Diet A **17**:5 (Jan) 1941

6 Wilder R M Nutritional Problems as Related to National Defense Am J Digest Dis **8**:243 (July) 1941 Williams R D and Mason H L Further Observations on Induced Thiamine (Vitamin B) Deficiency and Thiamine Requirement of Man Proc. Staff Meet. Mayo Clin **16**:433 (July 9) 1941

7 Blankenhorn M A., Vilter C F Scheinker I M and Austin, R S Occidental Beriberi Heart Disease, J A. M A. **131**:717 (June 29) 1946

8 Mills, C A Vitamin and Protein Requirements at Different Temperatures Am J Physiol **133**:390 (June) 1941 Environmental Temperatures and Thiamine Requirements, ibid. **133**:525 (July) 1941

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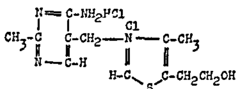


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8. Mills, C. A Vitamin and Protein Requirements at Different Temperatures, Am. J Physiol **133**:390 (June) 1941 Environmental Temperatures and Thiamine Requirements, ibid. **133**:5 5 (July) 1941

in more recent work by Kline, Friedman and Nelson[9] in which suboptimal levels of thiamine were used, evidence was presented to show that as the environmental temperature is increased, the daily requirement for thiamine is decreased

Diets rich in fat have a definite sparing action on the requirement of thiamine in both rats and dogs This is undoubtedly because fat metabolism does not require cocarboxylase The human diet may rarely undergo sufficient change in fat content to alter materially the thiamine requirement Cahill,[10] studying the urinary excretion of thiamine in human subjects, could observe *no increase when part of the carbohydrate was replaced* by fat

The two commonest methods in use today for the quantitative estimation of thiamine are the thiochrome method and the yeast fermentation method The detailed procedures are given in *Biological Symposia*[11] The rat assay procedure is still recognized as the official method and is described in the "Pharmacopeia of the United States," thirteenth revision

In table 1 are presented figures for the vitamin content of a few typical foods It is evident that only a few foods can be classified as rich sources of thiamine they include peas, beans oatmeal whole wheat and enriched flour and bread, lean pork and peanuts However one must not overlook the staple foods, such as milk, vegetables and fruits, which may contribute appreciable amounts of thiamine in the diet although the amount per unit of weight is relatively low It is well known that significant amounts of thiamine may be lost during the preparation of foods, because of the fact that the vitamin is readily soluble in water and easily destroyed by moist heat Under normal conditions there is probably little destruction of thiamine in the digestive tract although intestinal disturbance may seriously retard the absorption of this vitamin

The possible availability of thiamine synthesized by the bacterial flora of the gastrointestinal tract must not be overlooked although it appears that less thiamine is

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9 Kline O L Friedman L and Nelson E M The Effect of Environmental Temperature on Thiamine Requirement of the Rat J Nutrition **20**: 35 (Jan) 1945

10 Cahill W M Urinary Excretion of Thiamine on High Fat Diets J Nutrition **21**: 411 (April) 1941

11 Kline O L and Friedman L Micro-Biological Assay Methods of *Thiamine* Biological Symposia **12**: 65 85 1947

produced than some of the other B vitamins[12] It is also important to mention that the ingestion of live yeasts may render thiamine consumed in other foods unavailable for human beings (Parsons, Williamson and Johnson[13]) Severe thiamine deficiency can be produced in mice by feeding pyrithiamine the pyridine analogue of thiamine (Woolley and White[14]), but the

TABLE 1—*Vitamin Content of a Few Typical Foods*

Foods	Thiamine†	Riboflavin†	Niacin†	Pantothenic Acid†‡	Vitamin B6†‡	Biotin†‡	Folic Acid†‡
Apples	0 04	0 02	0.2	0 05	0 03	..	
Bananas,	0 09	0 06	0 6	0 18	0.30		0.01
Bread							
White (unfortified)	0 08	0 13	0.8	0 40	0.20		
White (fortified)	0 [illegible]4	0 15	2 2	0 40	0 [illegible]0		
Cabbage	0 07	0 06	0.3	0.18	0 29		0.01
Carrots.	0 07	0 06	0	0 24	0 19	0.002	0.01
Cheese	0 04	0 50	0.1	0.[illegible]	0.[illegible]0	0.002	
Cornmeal degerminated	0 1	0 06	0 9		0.[illegible]		0 02
Eggs whole fresh	0 12	0.34	0 1	2. 0		0 025	0 01
Meat							
Beef	0 12	0 15	5.2	1 10	0 40	0 004	0 02
Pork loin	1.04	0.20	4.4	1.50	0.60	0 005	0 01
Poultry chicken or turkey	0 10	0 18	8.0	0 90	0.20	0 01	
Liver pork or beef	0 27	2.80	16.1	5.[illegible]0	0.50	0 1	0 08
Milk whole fluid.	*0 04*	*0 17*	*0.1*	*0.[illegible]0*	*0.07*	*0 005*	
Oatmeal	0 65	0.14	1.1	1.[illegible]0	0.[illegible]5		0 03
Oranges	0 08	0 03	0.2	0.1			0 01
Peas fresh	0.36	0 18	2 1	0 60	0.05	0 00[illegible]	0.03
Peanuts roasted	0.[illegible]0	0 16	16 2	2.5	0.30		
Potatoes	0 11	0.04	1 2	0 40	0 16		0 01
Spinach	0 12	0.24	0 7	0 7	0.08	0 002	0 18
Tomatoes	0 06	0.04	0 6	0.37	0 07	0.002	0 01
Turnips	0 06	0 06	0.5	0.25	0 10	0 002	
Yeast Brewers dry	9 69	5.45	36.2	20 00	2.90	0.2	0.7
Wheat whole	0.56	0.12	5 6	1.30	0 40	0.005	0 05

Edible portion
† Values are given in milligrams per hundred grams
‡ Values for pantothenic acid pyridoxine (vitamin B_6) biotin and folic acid are based on data from only a limited number of samples Some of the values may be low because of incomplete liberation of the vitamin This is especially true in the case of pantothenic acid For example, Miands and Strong found 3 mg in 100 Gm of spinach after maximum liberation and only 0 7 mg by the old method. Dried yeast was observed to contain 40 mg and fresh eggs 5.0 mg

12 (*a*) Najjar V A. and Holth L. E Jr The Biosynthe s of Thia m ne in Man J A M A **123**: 683 (Nov 13) 1943 (*b*) Denko, C W Grundy W E Wheeler, N C. Henderson C R. Berryman, G H Friedemann, T E. and Youmans, J B The Excretion of B-Complex Vitamins by Normal Adults on a Restricted Intake, Arch. Biochem. **11**: 109 (Sept.) 1946

13 Parsons, H M Williamson A and Johnson M L. The Availability of Vitamins from Yeast I The Absorption of Thiamine by Human Subjects from Various Types of Bakers Yeast, J Nutrition **29**: 373 (June) 1945

14 Woolley D W and White, A. G C. Production of Thiamine Deficiency Disease by the Feeding of a Pyridine Analogue of Thiamine, J Biol. Chem. **149**: 285 (July) 1943

in more recent work by Kline, Friedman and Nelson[9] in which suboptimal levels of thiamine were used, evidence was presented to show that as the environmental temperature is increased, the *daily requirement for* thiamine is decreased

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11 Kline O L and Friedman L Micro-Biological Assay Methods of Thiamine, Biolog cal Symposia **12** 65 85 1947

dase and xanthine oxidase[18] A definite reduction in the tissue concentration of the latter enzymes has been observed in riboflavin deficient animals[19] Aside from retarded growth in young animals, other symptoms include dermatitis and cataract in rats and characteristic paralysis in chicks Work by Baum, Michaelree and Brown[20] indicates that the incidence of cataract in rats is increased if the diet supplies a small amount (1 to 2 micrograms daily) of riboflavin Phillips and Engel have shown a specific neuropathologic condition of the main peripheral nerve trunks in chicks on low riboflavin rations Similar changes were not observed in the rat until the riboflavin deficiency was aggravated by an increased fat content of the diet[21] Both acute and chronic riboflavin deficiency has been studied in dogs[22] On a diet very low in this vitamin a characteristic collapse syndrome and sudden death are observed in six to eight weeks Prolonged subsistence on a diet low in riboflavin leads to neurologic abnormalities accompanied with myelin degeneration of peripheral nerves and the posterior columns of the spinal cord Street, Cowgill and Zimmerman[22] have shown that opacities of the cornea may occur in the dog as well as in the rat

Severe riboflavin deficiency has been produced in the monkey with no evidence of corneal changes[23] The symptoms include lack of growth dermatitis and anemia Warkany and Schraffenberger[24] have described congenital defects and malformations of the skeleton of rats due to a low intake of riboflavin during the gestation period

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18 Hogness T R in A Symposium on Respiratory Enzymes Madison, Wis University of Wisconsin Press 1942 p 134

19 Axelrod, A. E. and Elvehjem, C. A The Xanthine Oxidase Content of Rat Liver in Riboflavin Deficiency J Biol. Chem **140** 725 (Sept) 1941

20 Baum H M Michaelree, J F., and Brown E B The Quantitative Relationship of Riboflavin to Cataract Formation in Rats, Science **95**:24 (Jan 2) 1942

21 Shaw, J H and Phillips, P H The Pathology of Riboflavin Deficiency in the Rat, J Nutrition **22** 345 (Oct.) 1941

22 Street H R Cowgill G R. and Zimmerman H M Further Observations of Riboflavin Deficiency in the Dog J Nutrition **23**:7 (July) 1941

23 Cooperman, J M Waisman H A. McCall K. B and Elvehjem, C A. Studies on the Requirements of the Monkey for Riboflavin and a New Factor Found in Liver J Nutrition **30**:45 (July) 1945

24 Warkany J and Schraffenberger E. Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency VI. The Preventive Factor J Nutrition **27**:477 (June) 1944

deficiency can be overcome by administration of an excess amount of thiamine

Recently a factor destructive of vitamin B_1 has been found in raw fish Green, Carlson and Evans[15] observed a type of paralysis in foxes fed diets containing 20 per cent fresh carp and identified the condition as a thiamine avitaminosis analogous to Wernicke's disease Further studies[16] on the mechanism of inactivation point to an enzymatic destruction Non enzymatic thiamine destroying factors have been found in seeds and in fern (Pteris aquilina) by Weswig, Freed and Haag[17]

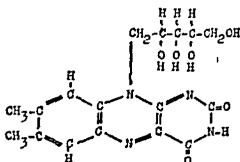


Fig 2.—Structural formula of d riboflavin.

RIBOFLAVIN

Riboflavin is a practically odorless orange yellow crystalline compound, which in water solution shows a characteristic yellow green fluorescence The empiric formula is $C_{17}H_{20}N_4O_6$ with the structural formula as shown in figure 2

This vitamin is rather heat stable, especially in acid mediums but extremely labile when exposed to light. In nature riboflavin may occur as such as riboflavin phosphate or as a constituent of specific flavoproteins These flavoproteins function as important enzymes in tissue respiration Enzymes known to contain riboflavin include cytochrome reductase d amino acid oxi-

15 Green R G Carlson W E. and Evans C A. A Deficiency Disease in Foxes Produced by Feeding Fish J Nutrition **21**: 243 (March) 1941

16 Spitzer E H Coombes A I Elvehjem C A and Wisnicky W Inactivation of Vitamin B1 by Raw Fish Proc Soc Exper Biol & Med **48**: 376 (Oct) 1941 Woolley, D W Destruction of Thiamine by a Substance in Certain Fish J Biol Chem **141**: 997 (Dec) 1941

17 Weswig P H Freed, A M and Haag J R. Anti Thiamine Activity of Plant Materials J Biol. Chem **165**: 737 (Oct) 1946

utilized Mannering and his co workers[29] observed that with suboptimal intakes of riboflavin rats receiving a diet high in dextrin or starch grew better than those receiving sucrose containing diets When the diet was high in lactose the riboflavin excretion in the feces was many times the dietary intake Denko and his co workers[12b] observed the fecal excretion in human subjects to be three times greater than the intake during periods in which there was a low riboflavin intake Hathaway and Lobb[30] observed a greater excretion when their subjects consumed natural foodstuffs than when they received purified diets although the intake was the same Sure and Dichek[31] have demonstrated in the case of rats that riboflavin has a pronounced beneficial effect on the economy of food utilization for the synthesis of body tissues In this connection it is



Fig 3 —Structural formula of nicotinic acid (niacin) (left) and nicotinic acid amide (niacin amide) (right)

interesting to note that Murlin and his co workers[32] reported that the biologic value of proteins in bread is improved in the presence of extra B vitamins

NIACIN

Niacin occurs as white needle like crystals is nonhygroscopic and stable in air and has the empiric formula $C_6H_5O_2N$ The structural formula of both the acid and the physiologically active amide are shown (fig 3)

The sensation of flushing and erythema of the skin which is often observed on administration of niacin is not produced by niacin amide Niacin is a comparatively weak acid and its alkaline salts in solution

29 Mannering G J Orsini D and Elvehjem, C A Effect of the Composition of the Diet on the Riboflavin Requirement of the Rat, J Nutrition 28: 141 (Sept.) 1944

30 Hathaway M L. and Lobb D E. A Comparison of Riboflavin Syntheses and Excretion in Human Subjects on Synthetic and Natural Diets, J Nutrition 32: 9 (July) 1946

31 Sure B and Dichek, M Riboflavin as a Factor in Economy of Food Utilization J Nutrition 21: 453 (May) 1941

32 Murlin, J R Marshall M E. and Kochakian, C D Digestibility and Biological Value of Whole Wheat Breads as Compared with White Bread, J Nutrition 22: 573 (Dec.) 1941

In human beings the symptoms include inflammation of the lips, fissures at the corners of the mouth, glossitis, dermatitis and vascularizing keratitis[8] The ocular symptoms first described by Sydenstricker and his co workers[26] appear to be constant and may appear before other symptoms of the deficiency There is still considerable difficulty in distinguishing the glossitis or riboflavin deficiency from that of pellagra pernicious anemia or iron deficiency and in distinguishing ocular ariboflavinosis from other conditions involving corneal vascularization

The riboflavin content of foods may be determined by measuring the growth response obtained in chicks or rats maintained on basal rations low in the vitamin but the more rapid microbiologic method of Snell and Strong[27] is now used extensively Chemical methods involving measurement of fluorescence are also being used[28] Riboflavin is widely distributed in plant and animal materials Liver, milk and green leafy vege tables may be considered the best and most reliable sources in the human dietary Seeds, which are so important as a source of thiamine, are poor sources of riboflavin

The Food and Nutrition Board recommends 1 8 mg of riboflavin as the daily allowance for men and the Food and Drug Administration has accepted 2 mg a day as the minimum daily requirement The limited values in table 1 show that one serving of liver will adequately meet the daily allowance that 1 quart of milk will supply the minimum requirement and that one serving of cheese or eggs will supply one fourth of the daily requirement There is also considerable evidence for the bacterial synthesis of riboflavin in the intestinal tract and that some of this riboflavin can be

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25 Sebrell W H and Butler R E Riboflavin Deficiency in Man Pub Health Rep **53** 2282 (Dec 30) 1938 Sydenstricker V P Geeslin L E Templeton C M, and Weaver J W Riboflavin Deficiency in Human Subjects J A M A **113**: 1697 (Nov 4) 1939

26 Sydenstricker V P Sebrell W H Cleckley H M and Kruse H D The Ocular Manifestations of Ariboflavinosis A Progress Note J A M A **114** 2437 (June 2) 1940

27 Snell E E and Strong F M A Microbiological Assay for Riboflavin Indust. & Engin Chem (Anal Ed) **11** 346 (June) 1939

28 Hodson A Z and Norris L. C A Fluorometric Method for Determining the Riboflavin Content of Foodstuffs J Biol Chem **131**: 621 (Dec) 1939 Conner R T and Straub G J Combined Determination of Riboflavin and Thiamine in Food Products Indust. & Engin Chem (Anal Ed) **13**: 385 (June) 1941

The high incidence of pellagra, when the diet contains much corn, is undoubtedly due not only to the low amount of niacin in corn but to the fact that the main protein in corn, zein, is very low in tryptophan A definite relationship between the niacin requirement and the protein part of the diet has been demonstrated in several different species and it is apparent that the conversion of tryptophan to niacin is the most limited in the dog An increased excretion of N'-methyl nicotinamide on administration of tryptophan has been observed in rats [37] and in human beings [38]

The early symptoms of pellagra are weakness lassitude, anorexia and indigestion, followed by sore and ulcerated mouth and diarrhea The typical dermatitis usually simplifies the diagnosis A more detailed sum mary of the symptoms has been made by Harris [39] and by Youmans [40] Spies Walker and Woods [41] have shown that infants and children also suffer from niacin deficiency in areas where pellagra is endemic, although typical lesions are seldom seen in early infancy Niacin is now widely used in the treatment of pellagra but its use is most successful in conjunction with other vitamins and specific natural foods

The activity of various compounds related in structure to niacin was investigated by Woolley and his co-workers [42] and it was concluded that only those compounds which may undergo oxidation or hydrolytic conversion to niacin are active in the dog Since that time some activity has been observed in human beings with *quinolinic acid pyrazine 2 3 dicarboxylic* acid and pyrazine monocarboxylic acid A paper by Dann, Kohn and Handler [43] summarized much of the

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37 Rosen F Huff J W and Perlzweig W A The Effect of *Tryptophane on the Synthesis of Nicotinic Acid in the Rat* J Biol. Chem. **163** 343 (April) 1946

38 Sarett H P and Goldsmith G A The Effect of Tryptophane *on the Excretion of Nicotinic Acid Derivatives in Human* J Biol Chem **167**:293 (Jan) 1947 Perlzweig W A Rosen F Levitas N and Robinson J The Excretion of Nicotinic Acid Derivatives After Ingestion of Tryptophane by Man ibid **167**:511 (Feb) 1947

39 Harris, S and Seale H Jr Clinical Pellagra St. Louis C V *Mosby Company 1941*

40 Youmans J B and Patton, E. W Nutritional Deficiencies Diagnosis and Treatment Philadelphia J B Lippincott Company 1941

41 Spies T D Walker A A and Woods, A W Pellagra in Infancy and Childhood, J A M A **113**:1481 (Oct. 14) 1939

42 Woolley D W *Strong F M, Madden R. J and Elvehjem* C A Antiblacktongue Activity of Various Pyridine Derivatives, J Biol. Chem. **124**:715 (Aug) 1938

43 Dann W J Kohn H I and Handler P The Effect of Pyrazine Acids and Quinolinic Acid on the V Factor Content of Human Blood and upon Canine Blacktongue, J Nutrition **20**:477 (Nov) *1940*

show a slightly alkaline reaction It is stable to autoclaving temperatures when in solution and shows no loss of activity when exposed to dry heat Owing to numerous objections to the term nicotinic acid niacin and niacin amide are used as synonyms for the acid and amide

In the body niacin functions as a component of two important coenzymes coenzyme I, or cozymase, *and coenzyme II, which are concerned in both gly* colysis and respiration[33] The structure of the two coenzymes is similar, differing only in the number of phosphoric acid units Coenzyme I is a diphosphopyridine nucleotide and coenzyme II is a triphosphopyridine nucleotide In niacin deficiency it is possible to demonstrate a decreased cozymase content of the liver and muscle tissue There has been some question about the cozymase content of the blood during deficiency but all workers[34] are now agreed that the change if demonstrable, is very slight It is thus *impossible to use this method in the diagnosis of* niacin deficiency

The dog was used as the experimental animal in all of the early work on the antipellagra vitamin Blacktongue in the dog was first described by Chittenden and Underhill and in 1922 Goldberger and his co workers concluded that blacktongue in dogs was analogous to pellagra in human beings Through the use of highly purified rations supplemented with the newer B vitamins it has been possible to demonstrate that the growing chick needs a dietary source of niacin for *optimum growth and for the prevention of chick* blacktongue[35] In the rat niacin is an essential nutrient only when the tryptophan content of the diet is low[36]

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33 Elvehjem C A *Relation of Nicotinic Acid to Pellagra* Physiol Rev **20**: 249 (April) 1940 Handler P The Present Status of Nicotinic Acid Ztschr f Vitaminforsch **19**: 394 1948

34 Kohn H I Klein J R and Dann W J The V Factor Content and Oxygen Consumption of Tissues from the Normal and Blacktongue Dog Biochem J **33** 1432 (Sept) 1939 Axelrod A E Spies T D and Elvehjem C A The Effect of a Nicotinic Acid Deficiency Upon the Coenzyme I Content of the *Human Erythrocyte and Muscle* J Biol Chem **138** 667 (April) 1941

35 Briggs G M Jr Mills R C Elvehjem C A and Hart, E B Nicotinic Acid in Chick Nutrition Proc Soc Exper Biol & Med **51**: 59 (Oct.) 194_

36 Krehl W A Sarma P S and Elvehjem, C A The Effect of *Protein on the Nicotinic Acid* and *Tryptophane Requirement* of the Growing Rat J Biol Chem **162**: 403 (March) 1946 Krehl W A Henderson L M de la Huerga J, and Elvehjem C A Relation of Amino Acid Imbalance to Niacin Tryptophane Deficiency in Growing Rats ibid. **166** 531 (Dec) 1946.

uct and this may account for much of the remainder The niacin requirement is not only dependent on the dietary tryptophan but part of the niacin requirement may be satisfied through bacterial synthesis in the digestive tract (Ellinger and Benesch[50]) The Food and Nutrition Board has suggested 12 to 18 mg as the daily allowance for an adult man and the minimum requirement has been set at 10 mg per day

One may readily ascertain from table 1 why pellagra will develop with diets containing high percentage of corn meal and patent flour These materials contain 1 to 1 5 mg per 100 Gm and one would have to consume 1 000 Gm to meet the minimum requirement which, of course is impossible In contrast to corn wheat contains 5 to 7 mg per 100 Gm and would be a reliable source of niacin if 80 to 90 per cent were not removed during the milling process[51] Whole oats are also low in niacin but barley is somewhat higher One serving of liver will supply the daily allowance and one serving of lean meat will supply over half of the daily requirement Since niacin is a very stable compound there is little destruction during cooking and the loss is negligible unless the cooking water is discarded Although milk and eggs are low in niacin these foods are important in the prevention of pellagra because they carry a good supply of tryptophan Certain compounds may function as antagonists to niacin for example 3 acetyl pyridine but these compounds apparently do not occur in nature in sufficient concentration to affect the niacin requirement

VITAMIN B_6

The term vitamin B_6' was first applied by György to a substance present in yeast which was active in the prevention and cure of a specific type of acrodynia in rats A specific compound was subsequently isolated in pure form almost simultaneously (1938) in five different laboratories and it was synthesized the following year by Harris and Folkers[52] Pyridoxine hydro-

50 Ellinger P B sch, R and Koy W W B osynth sis of Nicotinamide in the Human Gut Lancet 1: 43. (April 7) 1945

51 Teply L. J St ong F M and Elvehjem C. A The D stri bution of Nicotinic Acid in Foods J Nut t on 23: 417 (April) 194.

52. Harris, S A. and Folkers K. Synthesis of Vitamin B_6, J Am. Chem. Soc. 61: 1245 (May) 1939

work on these compounds, and from their results, as well as results in this laboratory, one may conclude that the activity of these compounds is greatly inferior to that of nicotinic acid

Since niacin is not required by the rat unless there is an amino acid imbalance in the diet, the dog originally used by Goldberger and his co workers for the assay of the antipellagra potency of foods is the only animal that has been used with any success Fairly accurate values can be obtained by comparing the growth response obtained by feeding a definite weight of food with that obtained after giving a standard dose of niacin [44] Chemical methods may be used on many foods and an improved method has been described by Dann and Handler [45] The most widely used method is the microbiologic method of Snell and Wright [46] and this method gives reliable results when proper precautions are taken for the release of the vitamin in certain foods The best sources of niacin include liver yeast lean meats and, to a lesser extent, peanuts potatoes and vegetables

It is difficult to establish an exact figure for the niacin requirement of human beings Balance experiments are complicated by the fact that excess niacin ingested is execreted in several different forms N' methyl nicotinamide is the product which has received most attention [47] Even when human subjects are given large doses of niacin, never more than 30 to 40 per cent of the dose can be accounted for [48]

However Knox and Grossman [49] have identified the corresponding 6 pyridone which is an oxidation prod-

44 Wa sman H A Mickelson O McKibbin J M and Elvehjem C A. Nicotinic Acid Potency of Food Mate ials and Certain Chemical Compounds J Nutrit on **19** 483 (May) 1940

45 Dann W J and Handler P The Quantitative Estimation of Nicotinic Acid in Animal Tissues J Biol Chem **140**: ^01 (July) 1941

46 Snell, E E and Wright L. D A M crob ological Method for the Determination of N cotinic Ac d J Biol Chem **139** 611 (June) 1941

47 Perlzweig W A Levy E D and Sarett H D N cotinic Acid Derivatives n Human Urine and The r Dete minat on J Biol Chem **136** 729 (Dec) 1940 Meln ck D Rob nson W D and Field H Jr Influence of the Excretion of Other Pyr dine Compounds on the Inter pretation of the Ur nary N cotinic Ac d Values ib d **136** 131 (Oct) 1940 Huff J W and Perlzweig W A N Methylnicot namide a Metabolite of Nicotinic Acid in the Urine ibid **150** 395 (Oct) 1943

48 Perlzweig W A Sarett H P and Margol s L H Stud es in Nicot nic Ac d Metabolism V A Te t for N cot n c Acid Defic ency in Man J A. M A **118** .8 (Jan 3) 1942

49 Knox, W E and Grossman W I The Isolation of the 6-Pyr done of N'-Methylnicotinamide from Urine J Biol Chem. **168** 363 (April) 1947

phate functions in the formation of tryptophan from indole and serine There also appears to be a functional relation between unsaturated fatty acids and the vitamin [59]

Pyridoxine has been shown to be essential in the nutrition of the rat [60] the chick,[61] the dog [62] and the pig [63] An acrodynia like syndrome characterized by edema, swelling and denuding of the paws and areas around the mouth and frequent thickening of the ears is associated with pyridoxine deficiency in the rat,[64] although it has been demonstrated [65] that a lack of this vitamin may cause retarded growth without the dermatitis The microcytic hypochromic anemia in dogs resulting from pyridoxine deficiency reported by Fouts and his co workers [6] has been amply confirmed [66]

No clearcut symptoms resulting from pyridoxine deficiency have been described in human beings Spies, Bean and Ashe [67] have reported an additional improvement in pellagrins with pyridoxine therapy after treatment with nicotinic acid riboflavin and thiamine Smith and Martin [68] observed a rapid and satisfactory healing of the typical lesions of cheilitis with vitamin B_6 therapy Although clinical treatment of such conditions as Parkinson's disease muscular dystrophy and paralysis agitans has been studied the results are not definite

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59 Birch T W The Relation Between Vitamin B and the Unsaturated Fatty Acid Factor J Biol Chem **124** 775 (Aug) 1938

60 Gyorgy P Sullivan M and Karsner H T Nutritional Dermatoses in Rats Proc Soc, Exper Biol, & Med **37** 313 (Nov) 1937

61 Hegsted D M Oleson J J Elvehjem C A and Hart, E B The Cartilage Growth Factor' and Vitamin B6 in the Nutrition of Chicks J Biol Chem **130** 423 (Sept) 1939

62 Fouts P J Helmer O M Lepkovsky S and Jukes, T H Production of Microcytic Hypochromic Anemia in Puppies on Synthetic Diet Deficient in Rat Antidermatitis Factor (Vitamin B) J Nutrition **16** 197 (Aug) 1938

63 Chick H Macrae T F Martin, H J P and Martin C. J The Water Soluble B Vitamins Other than Aneurin (Vitamin B) Riboflavin and *Nicotinic Acid Required by the Pig Biochem J* **32**:2207 (Dec) 1938

64 Gyorgy P and Eckardt R E Further Investigations on Vitamin B6 and Related Factors of the Vitamin B Complex in Rats, Biochem J **34**:1143 (Sept.) 1940

65 Conger T W and Elvehjem, C A The Biological Estimation of Pyridoxine (Vitamin B6) J Biol Chem. **138**:555 (April) 1941

66. Street, H R Cowgill G R and Zimmerman H M Some Observations of Vitamin B6 Deficiency in the Dog J Nutrition **21**: 75 (March) 1941 McKibbin J M Schaefer A E. Frost, D V and Elvehjem C A Studies on Anemia in Dogs Due to Pyridoxine Deficiency J Biol Chem **142**:77 (Jan) 1942

67 Spies, T D Bean W B and Ashe, W F A Note on the Use of Vitamin B6 in Human Nutrition J A. M A. **112**:2414 (June 10) 1939

68. Smith, S G., and Martin D W Cheilosis Successfully Treated with Synthetic Vitamin B6, Proc. Soc. Exper Biol. & Med. **43**:660 (April) 1940.

chloride is a white crystalline powder, slightly bitter in taste and odorless, and possesses the empiric formula $C_8H_{12}O_3NCl$

In 1944 it was shown[53] that two derivatives of pyridoxine, namely, pyridoxal and pyridoxamine were more active than the original compound tor the growth of certain lactic acid bacteria The three compounds have the structural formula shown in figure 4

All three compounds are highly active in curing vitamin B_6 deficiencies in animals All three forms occur in natural materials, although many tissues, particularly animal tissues, and yeast contain predominantly pyridoxal and pyridoxamine Phosphorylated pyridoxal functions as a coenzyme for those enzymes which decarboxylate tyrosine, arginine, glutamic acid, 'dopa, the precursor of melanin, and possibly other

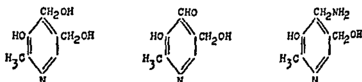


Fig 4—Structural formula (from left to right) pyridoxine pyridoxal and pyridoxamine

amino acids[54] It also functions in reactions involving transamination[55] and tissues from pyridoxine deficient rats show a reduced amount of transaminase[56] Pyridoxine is also closely related to tryptophan metabolism since Lepkovsky and Nielsen[57] observed abnormal pigment in the urine of pyridoxine deficient rats and this was later identified as xanthurenic acid Umbreit Wood and Gunsalus[58] have shown that pyridoxal phos

53 Snell E E and Rannefeld A N The Vitamin B6 Group III The Vitam n Activ ty of Pyridoxal and Pyr doxamine for Va ious Organ isms J Biol Chem **157** 475 (Feb) 1945

54 Gale E F The Bacterial Amino Ac d Decarboxylases in Nord F F Advances in Enzymology and Related Subjects New York Interscience Publishers Inc 1946 vol 6 p 1 Green D E L loir L F and Nocito V Transam nases J Biol Chem **161** 559 (Dec) 1945

55 O Kane D E and Gunsalus I C The Resolut on and Purification of Glutamic Aspartic Transam nase J B ol Chem. **170** 425 (Oct.) 1947

56 Ames S R Sarma P S and Elvehjem, C A. T ansaminase and Pyr dox ne Defic ency J B ol Chem **167** 135 (Jan) 1947

57 Lepkovsky S and Nielsen E A Green Pigment P oducing Compound in Urine of Pyridoxine-Deficient Rats, J B ol Chem. **144** 135 (June) 1942

58 Umbreit W W Wood W A and Gunsalus, I C The Activ ty of Pyridoxal Phosphate in Tryptophane Formation by Cell Free Enzyme Preparations J B ol Chem. **165** 731 (Oct.) 1946

thenic acid was achieved in 1940[75] The vitamin is now available as the dextrorotatory calcium salt, which occurs in fine dense white crystals that are odorless and slightly bitter in taste The empiric formula is $(C_9H_{16}NO_5)_2Ca$ The structural formula for the free acid is shown in figure 5

Pantothenic acid is fairly stable when subjected to moist heat especially at a neutral p_H but is destroyed by prolonged dry heat The compound is readily hydro lyzed into the two component parts in alkaline solution The compound is widely distributed in nature and recent work has shown that much of the vitamin may be present in bound forms Lipmann and his co work ers[76] have shown that pantothenic acid is related to enzymatic acetylation It was first shown[77] that a coenzyme was present in liver preparations which was

```
    H     H
    O  CH3 O    O  H  H  H  O
    |   |  |    \\ |  |  |  \\
H---C---C---C---C---N---C---C---C---OH
    |   |   |           |   |
    H   C   H           H   H
        H3
```

Fig 5 —Structural formula for pantothenic acid.

necessary for the acetylation of aromatic amines Later it was found[78] that the same coenzyme was needed for the acetylation of choline in brain tissue This coenzyme was prepared in concentrated form and observed to contain about 10 per cent pantothenic acid If panto thenic acid is related to all the biologic acetylations it has a very important function Riggs and Hegsted[79] have recently shown that acetylation of intraperitoneally administered p aminobenzoic acid in rats was definitely reduced when the animals were given a diet deficient in pantothenic acid The addition of the vitamin cor rected the abnormality

75 Stiller E. T Harris S A. Finkelstein J Keresztesy J C. and Folkers K Pantothenic Acid VIII The Total Synthesis of Pure Pantothenic Acid J Am Chem Soc. 62 1785 (July) 1940

76 Lipmann F, Kaplan N O Novelli G D Tuttle L. C and Guirard B M Coenzyme for Acetylation a Pantothenic Acid Derivative J Biol Chem 167:869 (March) 1947

77 Lipmann, F Acetylation of Sulfanilamide by Liver Homogenates and Extracts, J Biol. Chem 160:173 (Sept) 1945

78 Lipmann F and Kaplan, N O A Common Factor in the Enzymatic Acetylation of Sulfanilamide and of Choline, J Biol Chem. 162:743 (March) 1946

79 Riggs T R., and Hegsted, D M Effect of Pantothenic Acid Deficiency on Acetylation in Rats, J Biol. Chem. 172:539 (Feb.) 1948

enough to permit postulation of the action of the vitamin or to associate any one of these syndromes with specific lack of pyridoxine in the diet The human requirement is unknown, but animal experiments indicate that the vitamin B_6 requirement may be about the same as for thiamine, namely, about 1 5 mg a day

The most reliable method for determining the B_6 content of foods is probably the rat assay method,[68] although microbiologic methods involving Saccharomyces carlsbergensis and neurospora give values that are in reasonably good agreement with those obtained by rat assay[69] Among the best sources are rice, bran, liver, yeast, cereals legumes and milk Whole wheat contains about 0 4 mg in 100 Gm most meats 0 4 to 0 8 mg in 100 Gm when fresh[70] fresh vegetables about 0 2 mg in 100 Gm and milk about 1 mg per quart (liter) Swaminathan[71] found diets consumed in India to supply 3 5 to 5 mg a day

PANTOTHENIC ACID

The member of the B complex which prevented dermatitis in chicks was first called the filtrate factor' Although the so called filtrate fractions prepared from liver extract were effective in the prevention of black tongue in dogs pellagra in human beings and dermatitis in chicks, it was demonstrated as soon as niacin was accepted as the antipellagra factor that the activity of these fractions in the prevention of chick dermatitis was not due to the niacin present but to a separate and distinct vitamin Shortly thereafter, Woolley, Waisman and I[72] and Jukes[73] independently demonstrated that pantothenic acid which Williams and his co workers[74] had shown to be a growth factor for yeast as early as 1933 was similar to the chick antidermatitis factor The complete synthesis of panto

69 Stokes J L M crobiological Assay of the Vitamin B_6 Group Biol Symposia 12: 227 1947

70 Henderson L M Waisman H A and Elvehjem C A The Distribution of Pyridoxine (Vitamin B_6) in Meat and Meat Products J Nutrition 21: 589 (June) 1941

71 Swaminathan M A Method for the Estimation of Vitamin B_6 in Urine Indian J M Research 29: 561 (July) 1941

72 Woolley D W Waisman H A and Elvehjem C A Nature and Partial Synthesis of the Chick Antidermatitis Factor J Am Chem Soc 61: 977 (April) 1939

73 Jukes T H Pantothenic Acid and the Filtrate (Chick Antidermatitis) Factor J Am Chem Soc 61: 975 (Ap l) 1939

74 Williams R J Lyman C M Goodyear G H Truesdail J H and Haladay D Pantothenic Acid a Growth Determinant of Universal Biological Occurrence J Am. Chem. Soc. 55: 2912 (July) 1933

acid is widely distributed and that even restricted diets may not be low enough to cause a serious deficiency

No figures can be given for the daily human requirement The relatively high amount of pantothenic acid needed to produce good growth in rats on synthetic diets has led to the assumption that the requirement is considerably higher than that of some of the other B vitamins However, work in this laboratory indicates that the requirement for dogs can be satisfied with 0 10 mg per hundred grams ration a level similar to that of thiamine and riboflavin According to these results the human requirement cannot be above 5 mg a day

The pantothenic acid content of foods may be measured by growth experiments with chicks but the microbiologic methods[87] are now in more general use However in order to obtain the total pantothenic acid in foods when microbiologic methods are used it is necessary to treat the material with a liver enzyme and an intestinal phosphatase[88] Liver is one of the richest natural sources but meats cereals and milk are also reliable sources A few studies[89] have been made on the loss of pantothenic acid during cooking there is, as one would expect some loss the retention varying from 60 to 100 per cent Evidence is available to show that only about one half of the pantothenic acid in whole wheat is lost during the milling process

CHOLINE

Choline is a colorless viscous fluid and the more familiar choline chloride is a very hygroscopic white crystalline substance with a salty bitter taste The formula for choline is shown in figure 6 As expected from its chemical constitution the compound is not stable to alkali treatment but is stable to acids even at elevated temperatures

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87 Pennington D Snell E E, and Williams R J An Assay Method for Pantothenic Acid J Biol Chem. **134**:213 (Aug) 1940 Pelza M J, Jr and Port J R A Microbiological Assay Technic for Pantothenic Acid with the Use of Proteus Morgan ibid. **139**:111 (May) 1941 Strong F M Feeney R. E and Earle, A Microbiological Assay for Pantothenic Acid Indust. & Engin Chem (Anal Ed) **13**:566 (Aug) 1941 Jukes T H The Biological and Microbiological Assay of Pantothenic Acid, *Biol Symposia* **12** 53 1947

88 Neilands J B and Strong F M The Enzymatic Liberation of Pantothenic Acid Arch. Biochem **19**: 87 (Nov) 1948

89 Cover S Dilsaver E. M and Hays, R. M Retention of the B Vitamins in Beef and Lamb After Starving III. Pantothenic Acid, J Am. Diet. A **23**:693 (Aug) 1947

Rats placed on diets low in pantothenic acid grow very poorly and in a few weeks necrosis of the adrenal cortex develops which was first described by Daft and Sebrell[80] Changes in hair pigmentation (graying) have been observed in many laboratories when black or piebald rats were used Unna, Richards and Sampson[81] have published reproductions of photographs illustrating these fur changes in nutritional achromo trichia Schaefer, McKibbin and I[82] have produced acute deficiencies of pantothenic acid in dogs that are characterized by sudden collapse associated with decreased blood glucose, increased nonprotein nitrogen and lowered levels of blood chlorides Severe intussusception in the intestinal tract and fatty livers have also been observed Phillips and Engel[83] have reported specific neuropathologic changes of the spinal cord in chicks suffering from deficiency of pantothenic acid Wintrobe Miller and Lisco[84] have also observed neuropathologic changes in pigs on synthetic diets low in pantothenic acid and other members of the B complex

In spite of these interesting symptoms in experimental animals little is known about the real signifi cance of pantothenic acid in nutrition of human beings Spies and his co workers[85] concluded from studies based largely on values of pantothenic acid in the blood that pantothenic acid is essential to nutrition of human beings Krahnke and Gordon[86] have studied the excre tion of pantothenic acid in persons on different levels of intake However, no specific symptoms in human beings have been correlated with a deficiency of the vitamin This may be due to the fact that pantothenic

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80 Daft and Sebr ll c ted by Daft F S Sebrell W H Babcock S H Jr and Jukes T H Eff ct of Synthetic Pa tothen c Acid on Adrenal Hemorrhage Atrophy and Necrosis in Rats, Pub. Health Rep **55** 1333 (July 26) 1940

81 *Unna, K Richards G V and Sampson W L Studies on* Nutrit onal Achromotrich a n Rats J Nut tion **22**: 553 (Dec) 1941

82 Schaefer A E McKibbin J M and Elvehjem S A Pantothenic Acid Deficiency Stud es in Dogs J B ol Chem **143** 321 (April) 1942

83 Ph llips P H and Engel R W Some Histopatholog c Obser vat ons on Ch cks D ficient in the Chick Antidermat t s Factor or Pantothenic Acid, J Nutrition **18** *227* (Sept.) *1939*

84 Wintrobe M M M ller J L Jr and Lisco H The Relation of Diet to the Occurr nce of Ataxia and Degene ation of the Nervous System of Pigs Bull Johns Hopk ns Ho p **67** *377* (Dec) 1940

85 Sp es T D Stanbery S R W ll ms R J Jukes T H and Babcock S H Jr Pantothenic Acid in Human Nutrit n J A. M A **115** 523 (Aug 17) 1940

86 Krahnke H F and Gordon E S Pantothenic Acid in Human Nutrition J Clin. Invest gation to be published.

methyl groups McHenry[90] stated that there is evidence now that choline may function in at least three ways to stimulate the formation of phospholipids, to make possible the production of acetyl choline or to supply labile methyl groups

Extensive reviews have been published on choline and the reactions involved in biologic transmethylation by Best and Lucas[93] Jukes[94] and du Vigneaud[95]

Jukes[96] has shown that choline is one of the factors required in addition to adequate manganese to prevent slipped tendon in young turkeys Sure[97] reported that choline is indispensable for lactation in adult rats and in the prevention of paralysis in suckling rats Depression of the growth rate when choline is omitted from the diet has been observed in the case of the rat by Richardson, Hogan Long and Itschner[98] in the chick by Hegsted Mills Hart and me[99] and in the dog by *Schaefer McKibbin and me*[100]

The choline requirement even for the rat is difficult to establish, since the amount depends on the methionine and betaine content of the ration Most of the synthetic rations which are now used for experimental work contain 100 mg of choline in 100 Gm From this figure one might suggest that the human requirement would be less than 500 mg a day It has been estimated that the choline intake from an average *human diet may range from 250 to 600 mg* The problem of estimating accurately the choline content of food materials is also a difficult one since most salts of choline are very soluble in water except a few, like

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93 Best, C. H and Lucas C C Choline—Chemistry and Significance as a Dietary Factor in Harris R. S and Thimann V K. Vitamins and Hormones Advances in Research and Applications, New York Academic Press Inc. 1943 vol. 1 p 1

94 Jukes T H. Choline Ann Rev Biochem **16**: 193 1947

95 du Vigneaud V The Significance of Labile Methyl Groups in the Diet and Their Relation to Transmethylation in Harvey Lectures *194 1943* Baltimore Williams & Wilkins Company *1943* p. *39*

96 Jukes T H Prevention of Perosis by Choline J Biol. Chem. **134**: 89 (July) 1940

97 Sure B. The Essential Nature of Choline for Lactation and Growth of the Albino Rat, J Nutrition **19** 71 (Jan) 1940

98 Richardson, L. R Hogan A. G Long B and Itschner K. I The Number of Vitamins Required by the Rat, Proc. Soc. Exper Biol. & Med **46**: 530 (April) 1941

99 Hegsted D M Mills R. C Elvehjem, C. A and Hart E. B Choline in the Nutrition of Chicks J Biol. Chem **139**: 459 (April) 1941

100 Schaefer A. E. McKibbin, J M., and Elvehjem C. A. Importance of Choline in Synthetic Rations for Dogs, Proc. Soc. Exper Biol. & Med. **47**: 365 (June) 1941

Choline has been recognized for many years as a component part of the phospholipid lecithin, but its functional importance in nutrition was not apparent until Best demonstrated its role in the prevention of fatty livers in depancreatized dogs[90] Choline is now considered an important member of the B complex because most experimental animals, when placed on diets low in this compound and its precursors, show characteristic symptoms The most obvious changes include the development of fatty livers and hemorrhagic renal lesions The high requirement of the young rat for choline has been stressed by Griffith[91] who reported fatty degeneration of the liver renal lesions, ocular hemorrhages and regression of the thymus within ten days after the rats had been placed on a choline low but otherwise adequate, diet When the deficiency persists in animals which have fatty

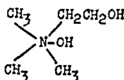


Fig 6—Structural formula for choline.

deposits in the liver cirrhosis will develop In the early stages this secondary change is also reversible if adequate choline is added to the diet

The function of choline must therefore be related to the mobilization of fatty acids in the body Experiments with the dog and the rat have demonstrated that neutral fat is involved since fatty livers induced by feeding high cholesterol diets do not respond to choline therapy The observations of du Vigneaud and his collaborators[92] that the methyl groups of choline as well as those of methionine and betaine are transferable in the animal organism has led to the postulation that one of the functions of choline is to supply labile

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90 McHenry E W Choline the B Vitamins and Fat Metabolism Biol. Symposia 5 177 1941

91 Griffith W H The Nutritional Importance of Choline J Nutrition 22 239 (Sept) 1941

92 du Vigneaud V Chandler J P Moyer A W and Keppel, D M The Effect of Choline on the Ability of Homocystine to Replace Methionine in the Diet J Biol Chem 131 57 (Nov) 1939 du Vigneaud V The Interrelationship Between Choline and Other Methylated Compounds Biol Symposia 5 234 1941

found in natural products is but slowly inactivated by alkali The pure biotin, however, shows appreciable lability to alkali Both the free and bound biotin are inactivated by oxidizing agents

It has been known for many years that a characteristic syndrome can be produced in rats fed diets containing rather high amounts of raw egg white Lease Parsons and Kelly [107] observed that the rabbit and the monkey also exhibited a characteristic dermatitis when fed rations rich in egg white As early as 1933 Parsons Lease and Kelly [108] concluded that the injury involved an interrelation between a positive toxicity and a relative absence of a protective factor

Gyorgy Rose, Eakin Snell and Williams [109] have established the presence of avidin (an albumin) as the biotin inactivating factor in egg white. Thus, it

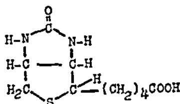


Fig 7—Structure of free biotin.

becomes apparent that egg white injury is due to the unavailability of biotin by virtue of being tied up with avidin, in which complex biotin cannot be absorbed from the intestine and is excreted in the feces Nielsen and I [110] using a more complete ration than had been used in the early work were able to demonstrate a biotin deficiency in the rat fed 10 per cent levels of egg white Typical symptoms of spectacled eye progressing to general alopecia and in the later stages the onset of a spasticity and final death of the animal

107 Lease, J G Parsons H T and Kelly E A Comparison in Five Types of Animals of the Effects of Dietary Egg White and of a Specific Factor Given Orally or Parenterally Biochem J **31**:433 (March) 1937

108 Parsons, H T Lease J G and Kelly E. The Cure of Dermatitis Due to Egg White by Various Foodstuffs, J Biol Chem. **100**: lxxvi (May) 1933

109 Gyorgy P Rose, C S, Eakin R E Snell, E. E. and Williams, R J Egg White Injury as the Result of Nonabsorption in Inactivation of Biotin Science **93**:4 7 (May 16) 1941

110 Nielsen, E. and Elvehjem C A Cure of Spectacle Eye Condition in Rats with Biotin Concentrates, Proc. Soc. Exper Biol. & Med. **48**:549 (Oct.) 1941

the periodide and the reineckate which have been used in quantitative estimations The most specific methods for determining choline are the estimation of acetyl choline after acetylation and the use of the microbiologic assay involving the cholineless mutant (no 34486) of Neurospora crassa These methods have been reviewed by Handler[101]

By far the best dietary source of choline is egg yolk while soybean meal, liver dried yeast pancreas, brain and kidney are good sources Most edible fats are very low in choline It should be pointed out that free choline is rarely found in food materials and is present mainly as complex phosphoric acid esters Most diets contain sufficient choline and its precursors to meet the ordinary needs However evidence is accumulating that some types of clinical cirrhosis are favorably affected by dietary treatment including choline and other vitamins together with a high protein diet

BIOTIN

Biotin was first recognized as a growth factor for yeast and was isolated by Kogl and Tonnis[102] in 1936 In 1940 du Vigneaud and his co workers[103] demonstrated that biotin the yeast growth factor, was the same as the anti egg white injury factor or vitamin H in animal nutrition Gyorgy had carried out extensive studies on the properties of vitamin H and after it was shown that biotin was identical with this factor du Vigneaud Hofmann Melville and Gyorgy[104] described the isolation of biotin from liver The structure was studied by du Vigneaud and co workers[105] and its synthesis was announced by Harris and his co workers[106] in 1943 Free biotin has the structure shown in figure 7 It is a very stable compound resisting autoclaving with strong mineral acids and in the form

101 Handler P The Determ nation of Choline n B ological Material B ol Symposia 12 361 1947

102 Kogl F, a d Tonnis B Plant Growth Substances XX The B os Problem Isolation of Crystalline B ot n from Egg Yolk Ztschr f phys ol. Chem 242 43 (Aug) 1936

103 du Vigneaud V Melville D B Gyorgy P and Ro C S On the Identity of V tamin H w th Biotin Sc ence 92: 62 (July 19) 1940

104 du Vigneaud V Hofmann K Melville D B and Gyorgy P Isolation of B otin (Vitamin H) from Liver J B ol Chem 140: 643 (Aug) 1941

105 du V gneaud V H fmann K and Melville, D B On the Structure of Biotin J Am Chem Soc 64 188 (Jan) 1942

106 Harris S A Wolf D E Mo ngo R and Folkers, K. Synthetic Biotin Science 97 447 (May 14) 1943

may be supplied by the intestinal bacteria Oppel[117] showed that the urinary excretion of biotin in human subjects exceeded that in the diet and in all cases the biotin content of the feces was considerably higher Sydenstricker and his co-workers[118] reported that dermatitis and changes in the color of the skin which responded to biotin were produced in human subjects by feeding diets with high levels of egg white Some have experienced difficulty in repeating these observations, but the variations may depend on the degree of intestinal synthesis In any case, there seems to be no difficulty in supplying an adequate amount of biotin in human beings on average diets

Biotin can be conveniently determined by use of microbiologic methods of assay in which responses in yeast growth (Snell Eakin and Williams[119]) or acid production by Lactobacillus casei (Shull Hutchings and Peterson[120]) are measured Biotin is rather ubiquitous in distribution but liver kidney yeast and egg yolk are the chief sources It is to be emphasized that in most tissues biotin is present in a bound' state in which it cannot be extracted by hot water and autolysis or acid hydrolysis must be employed to realize the true concentration of biotin in these instances Wright[121] summarized methods for the microbiologic determination of biotin as well as the compounds which inhibit the response of microorganisms to biotin

INOSITOL

Inositol is a crystalline substance with a sweet taste and is a hexahydroxycyclohexane comparable to the cyclic form of glucose The biologically active form of inositol is one of the optically inactive forms known as i inositol or meso inositol with the stereochemical structure shown in figure 8

It is a very stable compound resisting strong acid and alkali treatment It is found in plants where it

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117 Oppel T W Studies of Biotin Metabolism in Man, Am. J M Sc 204: 856 (Dec) 1942

118 Sydenstricker V P Singal S A Briggs A P DeVaughn, N M and Isbell H Observations on the Egg White Injury" in Man J A M A. 118: 1199 (April 4) 1942,

119 Snell E. E. Eakin, R. E. and Williams, R. J Quantitative Test for Biotin and Observation Regarding Its Occurrence and Properties, J Am Chem. Soc. 62: 175 (Jan) 1940

120 Shull, G M Hutchings B. L. and Peterson, W H A Microbiologic Assay for Biotin, J Biol. Chem. 142: 913 (Feb) 1942

121 Wright, L. D The Microbiological Determination of Biotin, Biol. Symposia 12: 290, 1947

were recorded Even the severe symptoms of spasticity were cured when excess biotin (in excess of that which unites with the avidin) was added to the diet With the synthetic diet without the egg white these workers were unable to demonstrate any signs of biotin deficiency, and it seems probable that under most conditions the rat can synthesize, through the medium of bacteria in the intestine, sufficient biotin for its requirement Biotin deficiency has been reported in the chick without resort to egg white diets which seems to indicate that very limited synthesis of biotin in the intestinal tract must prevail A typical dermatitis, involving the feet was observed by Hegsted and his co workers [111] to be characteristic of the deficiency in the chick and Patrick and his co workers [112] also noted similar dermatitis with turkeys on biotin deficient rations Waisman McCall and I [113] described the production of chronic biotin deficiency in the monkey with biotin deficient diets and acute biotin deficiency through the use of egg white

Recent work has established a more definite role for biotin in metabolism It apparently functions in the carboxylation of pyruvate to yield oxalacetate Working with Lactobacillus arabinosus Shive and his co workers [114] and Lardy and his associates [115] have shown that either oxalacetate or aspartate can partially replace biotin in the growth of this organism Another function of biotin can be replaced by oleic acid and Potter and I [116] have shown that when both aspartic acid and oleic acid are present good growth can be obtained in the absence of biotin

While rather definite requirements can be established for chicks, the requirement for many animals including man is difficult to establish since a large part

111 Hegsted D M Oleson, J J, Mills R C Elvehjem C A and Hart E B Stud es on a Dermatitis n Chicks Distinct from Pantothenic Acid Defic ency J Nut t on **20** 599 (Dec) 1940

112 Patrick H Boucher R V Dutcher R A and Knandel H C. B otin and Prevention of Dermatitis in Turkey Poults, Proc. Soc. Exper Biol & Med **48** 456 (Nov) 1941

113 Wa sman H A McCall K B and Elvehjem C A Acute and Chron c Biotin Deficienc es in the Monkey J Nutrition **29** 1 (Jan) 1945

114 Shive W and Rogers L. L. Involvement of Biotin in the B osynthesis of Oxalacetic and α-Ketoglutar c Acids J Biol. Chem **169** 453 (July) 1947

115 Lardy H A Potter R L and Elvehjem C A The Role of Biotin in Bicarbonate Ut li ation by Bacteria J B ol Chem **169**: 451 (July) 1947

116 Potter R. L and Elvehjem C A Biotin and the Met bolism of Lactobacillus Arab nosus J Biol Chem **172** 531 (Feb.) 1948

Sure[125] has presented data which indicate that inositol may be required by the lactating rat Martin, Thompson and de Carvajal-Forero[126] have injected rather low levels (10 mg per kilogram of body weight) of inositol into dogs and observed intestinal motility to be greatly increased A definite growth increment in the chick was obtained by feeding inositol in conjunction with a synthetic ration[127] In the rat inositol was observed to have an effect similar to lipocaic in preventing the fatty livers produced by the feeding of liver fractions or purified biotin preparations[128]

Inositol can be determined in tissues and foods by using a microbiologic assay employing a specific strain of yeast as the test organism[129] By this method of determination Williams and his co workers[130] have run large numbers of assays on various rat and beef tissues and observed spleen heart kidney brain, thyroid and testes to be especially high in inositol content

The requirements for inositol are not known Deficiency symptoms in mice have been cured by feeding 10 mg of inositol in 100 Gm of food Most purified rations which are now used for experimental purposes contain this level of inositol

Little is known regarding the role of inositol in human nutrition Perhaps the most interesting development is the report of Milhorat and Bartels[131] that inositol may improve the action of tocopherol in the treatment of progressive muscle dystrophy These authors suggested that inositol forms a complex with tocopherol in the intestinal tract and that this complex is necessary for normal creatine metabolism

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125 *Sure B Dietary Requirements for Fertility and Lactation* XXX Role of *p* Aminobenzoic Acid and Inositol in Lactation Science **94**: 167 (Aug 15) 1941

126 Martin G J Thompson M R. and de Carvajal Forero J Influence of Inositol and Other B Complex Factors upon the Motility of the Gastro-Intestinal Tract, Am J Digest. Dis. **8**: 290 (Aug) 1941

127 Hegsted D M Briggs, G M, Jr Mills R C Elvehjem C A. and Hart E B Inositol in Chick Nutrition Proc. Soc. Exper Biol. & Med **47**: 376 (Jan.) 1941

128 Gavin G and McHenry E W Inositol A Lipotropic Factor J Biol. Chem. **139**: 485 (May) 1941

129 Woolley, D W A Method for the Estimation of Inositol J Biol Chem. **140** 453 (Aug) 1941

130 Williams, R. J King A Mitchell, H K., and McMahan J R. Assay Method for Inositol Studies on the Vitamin Content of Tissues I Publication 4137 Austin Texas University of Texas Press, 1941 p 27

131 Milhorat, A. T., and Bartels W E. The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy Science **101**: 93 (Jan. 26) 1945

occurs in free form and as "phytin," a calcium magnesium salt of inositol phosphoric acid In the animal body inositol is found in muscle (accounting for the term 'muscle sugar"), brain, blood erythrocytes and eye tissues and as phytin in the red blood cells of chickens and turtles It also occurs in lipositol, which is a complex containing inositol monophosphate linked to galactose and combined with ethanolamine, tartaric acid, oleic acid and various saturated fatty acids Aside from its presence in biologic matter in the various forms, little is known about its specific function

The relation of inositol to the nutrition of animals was first indicated by the report of Woolley[122] who isolated the substance from liver and showed it to be

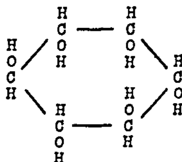


Fig 8—Structure of inositol

the constituent factor responsible for the cure of mouse alopecia Later Pavcek and Baum[123] were able to demonstrate a growth response and a cure of spectacled eye in rats The curative action and growth effect of inositol seems to be related to the amount and type of fat in the diet, since the syndrome was produced on fat free or low butter fat rations and not on those containing 14 per cent crisco A recent report by Lindley and Cunha[124] who worked with swine indicates a possible interrelationship between inositol and biotin, and this may explain why inositol was active in the prevention of the spectacled eye condition in rats

122 Woolley D W The Nature of the Antialopecia Factor Science 92 384 (Oct. 25) 1940

123 Pavcek P L and Baum, H M Inositol and Spectacled Eye in Rats Science 93: 502 (May 23) 1941

124 Lindley, D C and Cunha T J Nutritional Significance of Inositol and Biotin for the Pig J Nutrition 32: 47 (July) 1946

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126 Martin G J Thompson M R. and de Carvajal Forero, J Influence of Inositol and Other B Complex Factors upon the Motility of the Gastro-Intestinal Tract, Am J Digest. Dis. **8** 90 (Aug) 1941

127 Hegsted D M Briggs G M Jr Mills R C Elvehjem C. A. and Hart E B Inositol in Chick Nutrition Proc. Soc. Exper Biol & Med **47**: 376 (Jan) 1941

128 Gavin G and McHenry E W *Inositol A Lipotropic Factor* J Biol Chem. **139** 485 (May) 1941

129 Woolley, D W A Method for the Estimation of Inositol J Biol Chem **140**: 453 (Aug) 1941

130 Williams, R. J King A Mitchell, H K and McMahan J R. Assay Method for Inositol Studies on the Vitamin Content of Tissues I Publication 4137 Austin Texas University of Texas Press, 1941 p 27

131 Milhorat, A. T., and Bartels W E. The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy Science **101**: 93 (Jan. 26) 1945

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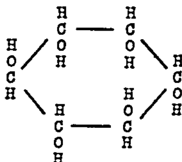


Fig. 8.—Structure of inositol.

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122. Woolley, D. W. The Nature of the Antialopecia Factor. Science 92: 384 (Oct. 25) 1940.
123. Pavcek, P. L., and Baum, H. M. Inositol and Spectacled Eye in Rats. Science 93: 502 (May 23) 1941.
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125 Sure B Dietary Requirements for Fertility and Lactation XXX Role of *p* Aminobenzoic *Acid and Inositol in Lactation, Science* **94** 167 (Aug 15) 1941

126 Martin G J Thompson M R. and de Carvajal Forero, J Influence of Inositol and Other B Complex Factors upon the Mot l ty of the Gastro-Intestinal T act, Am. J D gest. D s. 8 90 (\ug) 1941

127 Hegsted D M Briggs, G M Jr Mills R C. Elv hjem, C A., and Hart E B Inositol n Chick Nutrition Proc. Soc. Exper B ol. & Med. **47** 3 6 (Jan) 1941

128 Ga in G and McHenry E W Inositol A Lipotropic Factor J B ol. Chem **139** 485 (May) 1941

129 Woolley, D W A Method for the Estimation of Inos tol J Biol. Chem. **140**: 453 (Aug) 1941

130 Williams, R. J K ng A Mitchell, H K and McMahan J R. Assay Method for Inositol Studies on the Vitamin Content of Tissues I Publication 4137 Austin Texa Univ rsity of Texas Press, 1941 p 27

131 M lhorat, A. T., and Bartels W E. The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy Science **101**: 93 (Jan. ?6) 1945

PARA-AMINOBENZOIC ACID

Another factor which is often included in the B complex is para aminobenzoic acid (fig 9)

It was first recognized as an essential metabolite when Woods[132] discovered the antagonistic action between this compound and sulfanilamide and the consequent identification of para-aminobenzoic acid as a bacterial growth factor[133] The relation of sulfonamide drugs and para aminobenzoic acid has been reviewed by Welch[134] The report by Ansbacher[135] *that the graying of the fur observed in rats on certain* synthetic rations could be cured by the administration of 3 mg of para aminobenzoic acid daily stimulated much interest in this compound as an animal factor

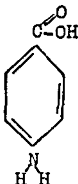


Fig 9—Structure of para aminobenzoic acid.

Numerous papers have appeared dealing with this compound as it affects hair color growth and lactation in rats and other animals but most of the results are conflicting Briggs and his co workers[136] observed a growth response on adding para-aminobenzoic acid to purified rations for chicks but suggested that it acts indirectly by stimulating the production of unknown

132. Woods, D D The Relation of *p*-Aminobenzoic Acid to the Mechanism of Action of Sulphanilamide, Brit. J Exper Path. **21** 74 (April) 1940

133 Rubbo, S D and Gillespie, J M Para Aminobenzoic Acid as a Bacterial Growth Factor Nature **146** 838 (Dec. 28) 1940

134 Welch, A. D Interference with Biological Processes Through the Use of Analogs of Essential Metabolites, Physiol Rev **25** 687 (Oct.) 1945

135 Ansbacher S *P* Aminobenzoic Acid Vitamin Science **93** 164 (Feb 14) 1941

136. Briggs G M Jr Luckey T D, Mills, R. C. Elvehjem C A. and Hart, E. B Effect of *p*-Aminobenzoic Acid when Added to Purified Chick Diets Deficient in Unknown Vitamins, Proc. Soc. Exper Biol. & Med. **52** 7 (Jan) 1943

vitamins through intestinal synthesis The possible role of para-aminobenzoic acid in the treatment of gray hair in human beings has been studied by Brandaleone and his associates,[137] who reported that in a group of 19 elderly persons with gray hair only 2 persons showed a significant color change during a period of intensive vitamin therapy At present there appears to be no clearcut evidence that this metabolite must be supplied preformed in the diet of human beings The contradictory results which have been obtained may be due to the fact that this compound is a constituent of the folic acid molecule

The most striking observation regarding para-aminobenzoic acid is its chemotherapeutic effect on typhus[138] and Rocky Mountain spotted fever[139]

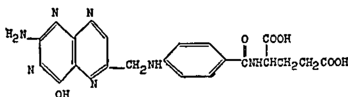


Fig 10—Structure of folic acid (pteroyl glutamic acid)

FOLIC ACID

Chemically folic acid is N-[4-{[2-amino-4-hydroxy-6 pteridyl)methyl]amino}benzoyl] glutamic acid, or pteroyl glutamic acid[140] It is a yellow compound sparingly soluble in water and has the structure shown in figure 10 This molecule contains three different groups the pteridine part para aminobenzoic acid and glutamic acid The part consisting of the pteridine and para aminobenzoic acid is called pteroic acid

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137 Brandaleone H Mann E. and Steele J M Effect of Calcium Pantothenate and Para Aminobenzoic Acid on the Gray Hair of Humans Proc. Soc Exper Biol. & Med **53** 47 (May) 1943

138 Yeomans A Snyder J C Murray E S Zarafonetis, C. J D and Ecke R. S The Therapeutic Effect of Para Aminobenzoic Acid in Louse Borne Typhus Fever J A. M A. **126**:349 (Oct. 7) 1944

139 Flinn L. B Howard J W Todd C W and Scott, E G Para Aminobenzoic Acid Treatment of Rocky Mountain Spotted Fever J A. M A **132** 911 (Dec. 14) 1946

140 Angier R B, Boothe J H Hutchings, B L. Mowat, J H Semb, J Stockstad E L R SubbaRow Y Waller C W Cosulich D B Fahrenbach M J Hultquist M E., Kuh, E. Northey E. H Seeger D R. Sickels J P and Smith J M Jr Synthesis of a Compound Identical with the L Casei Factor Isolated from Liver Science **102**:227 (Aug 31) 1945

Folic acid is widely distributed in nature, both in free form and in compounds with added glutamic acid, such as pteroyl triglutamic acid (fermentation factor) and pteroyl heptaglutamate (vitamin B_c conjugate)[141]

In light of our present knowledge it is apparent that folic acid deficiencies were observed over ten years ago in monkeys (Day and his co workers[142]) and in chicks (Hogan and Parrott[143]) Greatest progress in the isolation of this vitamin was made when it was recognized that a growth factor was needed for the *growth of Lactobacillus casei and related organisms*[144] and that concentrates of this factor were active for growth and hemoglobin production in chicks fed purified rations[145]

Most knowledge concerning the function of folic acid has come from studies on bacterial metabolism Nimmo Smith and Woods[146] have shown that all organisms requiring para aminobenzoic acid grow equally well when given folic acid although the required molar concentration of folic acid was greater than that of para aminobenzoic acid Folic acid also acted as an antisulfonamide agent with these organisms although the activity differed from that of para aminobenzoic acid in that it was noncompetitive Stokes[147] and Lampen and Jones[148] have suggested that folic acid

141 Pfiffner J J Binkley S B Bloom E S Brown R A Bird O D Emmett A D Hogan A G and O Dell B L Isolation of the Ant anemia Factor (V tamin B) n Crystalline Form from Liver Science **97** 404 (April 30) 1943 Pfiffner J J and Hogan A G The Newer Hematopoietic Factors of the Vitamin B Complex in Harris R S and Th mann K V Vitamins and Hormones New York Academic Press Inc 1946 vol. 4 p 1

142 Day P L Langston W C Darby W J Wahlen J G and Mims V Nut itional Cytopenia in Monkeys Receiv ng the Goldberger Diet J Exper M d **72** 463 (Oct.) 1940

143 Hogan A. G and Parrott E M Anemia in Ch cks Caused by Vitamin D fic ency J Biol Chem **132** 507 (Feb) 1940

144 Snell E E and Pete son W H Growth Facto s for Bacteria X Additional Facto s Requ ed by Certain Lact c Acid Bacteria J Bact **39** 273 (March) 1940 M tchell H K Snell E E and Williams, R J The Concentrat on of Folic Ac d Commun cat ons to the Editor J Am. Chem Soc **63** 2284 (Aug) 1941

145 Hutchings B L. Bohonos N Hegsted D M Elvehjem C A and Peterson W H Relat on of a Growth Factor Required by Lactobacillus Ca e to the Nutrition of the Ch ck J B ol Chem. **140** 681 (Aug) 1941

146 N mmo Sm th R H and Woods D D P Am nob nzo c Acid and Fol c Ac d in Bacterial Growth n Abst acts of Commun cat ons Seventeenth Internat onal Phy iolog cal Cong ess p 328

147 Stokes J L. Substitut on of Thymine for Fol c Ac d in the Nutrit on of Lactic Ac d Ba t r a J Bact *48* *201* (Aug) *1944*

148 Lampen J O and Jones M J The G owth P omoting and Antisulfonam de Activ ty of p-Am nobenzo c Ac d Pte oylglutamic Acid and Related Compounds for Lactob cillu Arab nosus and Streptobact rium Plantarum, J Biol Chem **170** 133 (Sept) 1947

functions as a prosthetic group in an enzyme concerned with the synthesis of thymine or related compounds

Today it is well established that synthetic folic acid is required for growth and blood formation in chicks,[149] monkeys[150] and fox and mink[151] Rats do not require preformed folic acid in the diet until the synthesis of this compound by intestinal bacteria is reduced through the use of sulfonamide drugs[15] Similarly dogs grow and regenerate hemoglobin very well on diets devoid of folic acid, although a deficiency can be produced by allowing blacktongue to develop in the dog several times[153] A folic acid deficiency has been produced in the pig[154] and in the mouse[155] by using an antagonist of folic acid In most cases the three forms of folic acid show equivalent activity although there is some evidence that the pteroyl heptaglutamic acid is not as active in the monkey as pteroyl glutamic acid[150]

The human being is apparently similar to the rat and dog in that the requirement is satisfied by intestinal production except under disturbed conditions Attempts to deplete volunteer subjects of their tissue reserves of folic acid by supplying diets adequate in other essential nutrients but low in folic acid have not been successful In spite of this fact the activity of synthetic folic acid in various types of macrocytic anemia in relapse has repeatedly been demonstrated The activity

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149 Luckey T D Moore P R Elvehjem C A, and Hart, E B The Activity of Synthetic Folic Acid in Purified Rations for the Chick Science **103** 682 (June 7) 1946

150 Day P L Mims V Totter J R Stokstad E L. R Hutchings B L., and Sloane N H The Successful Treatment of Vitamin M Deficiency in the Monkey with Highly Purified Lactobacillus Casei Factor J Biol Chem **157** 423 (Jan) 1945 Cooperman J M Elvehjem C A McCall K B and Ruegamer W R Folic Acid Active Compounds in the Nutrition of the Monkey Proc Soc Exper Biol. & Med. **61** 92 (Jan) 1946

151 Schaefer A E. Whitehair C K and Elvehjem C A Purified Rations and the Importance of Folic Acid in Mink Nutrition Proc. Soc. Exper Biol. & Med **62** 169 (June) 1946 Purified Rations and the Requirement of Folic Acid for Foxes Arch Biochem **12**: 349 (March) 1947

152 Nielsen E, and Elvehjem C A: The Growth Promoting Effect of Folic Acid and Biotin in Rats Fed Succinylsulfathiazole J Biol Chem. **143**: 713 (July) 1942 Welch A F and Wright L. D The Role of "Folic Acid" and Biotin in the Nutrition of the Rat J Nutrition **25**: 555 (June) 1943

153 Krehl, W A Torbet N de la Huerga J and Elvehjem, C. A. Relation of Synthetic Folic Acid to Niacin Deficiency in Dogs, Arch. Biochem **11**: 363 (Oct) 1946

154 Welch, A D Heinle, R. W Sharpe G George, W L., and Epstein, M Chemical Antagonism of Pteroylglutamic Acid on a Pig Hematopoietic Effect of Extrinsic and Intrinsic Factors, Proc. Soc. Exper Biol & Med **65**: 364 (June) 1947

155 Franklin, A L Stokstad, E. L. R and Jukes, T H Acceleration of Pteroylglutamic Acid Deficiency in Mice and Chicks by a Chemical Antagonist Proc. Soc. Exper Biol. & Med. **65**: 368 (June) 1947

of pteroyl glutamic acid was first demonstrated during the latter part of 1945 and the extensive clinical studies have been summarized by Spies and his co workers,[156] Darby[157] and Cartwright[158] Darby[157] has also described the effects of pteroyl glutamic acid on the gastrointestinal manifestations of sprue and related syndromes Since commercial preparations of the classic pernicious anemia factor contain practically no folic acid[159] and since a pure substance, vitamin B_{12}, which is active in very small amounts in the treatment of *pernicious anemia*, has now been isolated[160] it is clear that the effect of folic acid may not be direct or that its effect is closely related to additional factors It is entirely possible that extensive use of vitamin B_{12} in the treatment of anemia in human beings will bring out conditions that will respond only to folic acid Such a condition has been obtained in the dog on low protein-low *niacin diets*[161]

It is difficult to suggest any figures for the folic acid requirement of human beings Clinical responses have been obtained with 2 to 10 mg but this intake must be considerably higher than the daily requirement On the basis of the requirements for other animals a figure of 0 1 to 0 2 mg per day may be reasonable

Microbiologic methods have been used almost exclusively for the estimation of the folic acid content of foods although chick assays have been used for comparison In fact it was the discrepancy between the chick assay and the microbiologic assay which led to the isolation of the conjugate which has activity for the chick but not for bacteria[162] In 1942 Cheldelin and

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156 Spies T D The Use of Pteroylglutamic Acid (Liver L Casei Factor Folic Acid) in Clinical Studies Ann Rev Biochem **16** 387 1947 Berry L J and Spies T D The Present Status of Folic Acid Blood **1**: 271 (July) 1946

157 Darby W J The Physiological Effect of the Pteroyl Glutamates in *Man—With Particular Reference to Pteroylglutamic Acid (P G A)* in Harris R S and Thimann K V Vitamins and Hormones New York Academic Press Inc 1947 vol 6 p 119 Darby W J The Treatment of Nutritional Anemias with Folic Acid in Symposia on Nutrition of the Robert Gould Research Foundation Cincinnati Ohio 1947 vol 1 p 61

158 *Cartwright G E Dietary Factors Concerned in Erythropoiesis* Blood **2** 111 (March) 256 (May) 1947

159 Stokstad E L R and Jukes T H Absence of Appreciable L Casei Factor Effect of Antipernicious Anemia Liver Extract Proc Soc. Exper Biol & Med **62** 112 (June) 1946

160 Rickes E L Brink N G Koniuszy F R Wood T R and Folkers K Crystalline Vitamin B_{12}, Science **107**: 396 (April 16) 1948

161 Ruegamer W R Brickson W L Torbet N J and Elvehjem C A Response of Dogs to Liver Extracts Containing the Pernicious Anemia Factor J Nutrition **36** 425 (Oct) 1948

16 Binkley S B Bird O D Bloom E S Brown R. A Calkins D G Campbell C J Emmett, A D and Pfiffner J J On the Vitamin C Conjugate in Yeast Science **100** 36 (July 14) 1944

Williams[163] reported the folic acid content of many foods, but at that time it was necessary to use a standard of assumed potency since the crystalline vitamin was not available Cheldelin and his co workers[164] found taka diastase the most effective of several enzymes studied for the release of folic acid but later work has shown that a water extract of fresh hog kidney as described by Bird and his co workers[165] gives higher results Olson and his co-workers[166] have studied some of the difficulties encountered in the release of folic acid in liver homogenates The results of a preliminary report[167] on the folic acid content of foods show liver and deep green leafy vegetables to be very high and green vegetables cauliflower, kidney, muscle meat and wheat cereals to be high in folic acid values Preliminary results also indicate that the loss of folic acid during cooking may be very high, although *improved methods for the release of conjugated forms* may alter the results somewhat There is also considerable loss in vegetables during storage at room temperature

COMMENT

So far, ten members of the B complex have been described and a pure compound has been associated with each vitamin During the early studies on the additional factors required by the chick Briggs and his co workers[168] described two factors one which showed greatest activity in the promotion of growth and one which was more active in stimulating feather production On the basis of microbiologic assays, which did not include enzymatic treatment for the complete release of folic acid both appeared to be different from the bacterial growth factor (folic acid), and they

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163 Cheldelin V H and Williams R. J *Studies on the Vitamin Content of Tissues II The B Vitamin Content of Foods*, Publication 4237 Austin Texas University of Texas Press 1942 p 105

164 Cheldelin, V H Eppright, M A Snell, E E. and Guirard, B M Studies on the Vitamin Content of Tissues II. Enzymatic Liberation of B Vitamins from Plant and Animal Tissues Publication 4237 Austin Texas University of Texas Press 194 p 15

165 Bird, O D *Bressler F Brown* R. A, *Campbell, C J.*, and Emmett, A D The Microbiological Assay of Vitamin B Conjugate, J Biol Chem. 1[illegible]0 631 (Aug) 1945

166 Olson O E. Fager E. E. C Burris R. H., and Elvehjem, C A. Folic Acid Activity in Homogenates of Rat Liver J Biol. Chem. 174: 319 (May) 1948

167 Olson O E. Burris, R. H, and Elvehjem, C. A A Preliminary Report *of the Folic Acid Content of Certain Foods, J Am.* Diet. A. [illegible]3: [illegible]00 (March) 1947

168 Briggs G M Jr Luckey T D Elvehjem, C. A. and Hart, E. B Studies on Two Chemically Unidentified Water Soluble Vitamins Necessary for the Chick, J Biol. Chem. 148: 163 (April) 1943

were designated B_{10} and B_{11} When synthetic folic acid became available an adequate amount added to synthetic rations produced excellent growth feathering and hemoglobin production Folic acid appears to replace the two factors, although part of the effect may be indirect The exact relation of folic acid to vitamin B_{10} and vitamin B_{11} will have to await new technics

VITAMIN B_{12}

Rickes and his associates[169] have isolated from liver a crystalline compound which is highly active in patients with Addisonian pernicious anemia[169] On the basis of the aforementioned terminology, this compound has been called vitamin B_{12} This compound is also active for the growth of Lactobacillus lactis[170] The availability of this compound for unrestricted experimental work will do much to establish the exact relation of folic acid to macrocytic anemias

ADDITIONAL FACTORS

The existence of several additional factors is evident from studies with a number of different animal species In the case of rats, it has been shown that liver and liver preparations will stimulate the rate of growth of these animals when they are maintained on a corn soybean ration[171] or fed a basal ration with added thyroid[172] Cary and his co workers[173] have developed an assay for an unknown factor called factor X, by prolonged extraction of the casein used in the ration and by depleting the young by feeding their mothers a diet deficient in factor X Commercial liver extracts were observed to contain this factor A growth response can be obtained in chicks fed a corn soybean ration by adding fish products[174] or preparations from

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169 West R Activity of Vitamin B_{12} in Addisonian Pernicious Anemia Science **107** 398 (April 16) 1948

170 Shorb M S Activity of Vitamin B_{12} for the Growth of Lactobacillus lactis Science **107** 397 (April 16) 1948

171 Sporn E M Ruegamer W R and Elvehjem C A Growth and Reproduction in Rats on Synthetic Rations Proc. Soc. Exper Biol & Med **65**: 5 (May) 1947

172 Ershoff B H Effects of Liver Feeding on Growth and Ovarian Development in the Hyperthyroid Rat Proc Soc. Exper Biol & Med **64** 500 (April) 1947 Betheil J J Wiebelhaus V D and Lardy H A Studies of Thyroid Toxicity I A Nutritional Factor Which Alleviates the Toxicity of Ingested Thyroid Substance J Nutrition **34**: 431 (Oct) 1947

173 Cary C A Hartman A M Dryden L P and Likely G D An Unidentified Factor Essential for Rat Growth Fed Proc **5**: 128 (Feb) 1946

174 Berry E P Carrick C W Roberts R. E and Hauge S M Condensed Fish Press Water and Fish Liver Meal in Chick Rations Poultry Sc. **24** 270 (May) 1945

cow manure[175] Chicks maintained on a similar ration also respond to the injection of very small quantities of liver concentrates rich in the pernicious anemia factor[176] When dogs are placed on diets deficient in niacin and folic acid and containing a sulfonamide drug, the animals finally fail to respond to the addition of these two vitamins Highly purified liver concentrates given intramuscularly are highly effective in producing growth and hematopoietic responses[161] Whether the same factor is concerned in all these reactions and whether vitamin B_{12} will function in any of the conditions remains to be determined

Recent studies show that in monkeys fed highly purified rations deficient in folic acid or riboflavin a type of anemia develops which responds only when fresh liver or raw milk is given[23] In this case liver concentrates are inactive which indicates that the factor is separate and distinct from those previously mentioned[177] This factor may be related to one of the two factors observed to be needed by the fox and mink for normal growth and development[178]

The availability of the several synthetic water-soluble vitamins has been of the greatest value in clinical practice and also for the fortification of certain foods but the common foods still remain the best source of these vitamins in practical nutrition Aside from the gustatory significance of properly prepared natural foods the greatest value obtained from their consumption is that they supply the unknown factors along with the known All the known water soluble vitamins may be obtained from natural foods through proper selection The selection is not an easy task even with the modern methods of food production and distribution Some of the modern methods of processing increase rather than decrease the difficulties Often more emphasis is placed on the mere use of natural foods than on the proper combination of these foods The few values

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175 Rubin, M and Bird, H R. A Chick Growth Factor in Cow Manure Its Non Identity with Chick Growth Factors Previously Described J Biol. Chem **163**: 393 (May) 1946

176 Nichol C. A Robblee A R. Cravens, W W and Elvehjem, C. A. Activity of Anti Pernicious Anemia Preparations in Chicks, J Biol Chem. **170**: 419 (Sept.) 1947

177 Ruegamer W R. Sporn, E. M Register U D., and Elvehjem, C. A. Distribution and Fractionation of the Monkey Anti-Anemia Factor J Nutrition, **36**: 405 (Sept.) 1948.

178. Schaefer A. E. Whitehair, C. K., and Elvehjem, C. A. Unidentified Factors Essential for Growth and Hemoglobin Production in Foxes J Nutrition **35**: 147 (Feb.) 1948. Schaefer A. E. Tove, S B Whitehair C. K., and Elvehjem, C. A. The Requirement of Unidentified Factors for Mink, ibid. **35**: 157 (Feb.) 1948.

given in table 1 clearly indicate the fallacy of this emphasis Different natural foods differ greatly in the amount of any given vitamin which they contain Thus, apples contain 0 04 mg and pork loin 1 0 mg of thiamine in 100 Gm Eggs supply 0 1 mg and peanuts 16 mg of niacin in 100 Gm In addition, any one food may show large variations in the amount of the different B vitamins present. Thus, oatmeal contains 0 65 mg of thiamine, but only 0 14 mg of riboflavin, in 100 Gm, while liver contains 0 27 mg of thiamine and 2 8 mg of riboflavin in 100 Gm

There has been an increasing interest in eliminating the effect of this variation by prescribing vitamin concentrates In other words, a tablet or a capsule may supply the daily requirement of the vitamins, and

TABLE 2.—*Vitamin Content of a Few Commercial Concentrates*

Sample	Thiamine	Riboflavin	Niacin	Vitamin B_6	Pantothenic Acid
A	5.0	3.0	20.0	0.5	2.0
B	1.0	1.0	0 15	0 03	0.2
C	2.5	2.5	20.0	0.5	
D	1.0	0 1			
E	1.5	2.0	20.0	0.2	1.0
F	0.6	0 1			
G	1.5	2.0			
H	1.5	1.0			
I	1.0	0.23	5.0		..

Values are given in milligrams per unit of product

any pleasing combination of foods may be consumed for the rest of the day A survey conducted at the time the first Handbook of Nutrition" was prepared showed that the concentrates varied to a much greater extent than do natural foods A resurvey of typical concentrates on the market shows that this variation has decreased to a considerable extent but one still finds products varying from 0 6 to 5 mg of thiamine per unit of product Niacin values vary from 0 15 to 20 mg These products are useful in the treatment of specific deficiencies, but unless they are properly used they give no greater security than the proper combination of natural foods Thus, one not only needs to identify all the essential vitamins, but one must give consideration to distribution of these factors in food and food preparations as well as to the daily requirements of human beings

CHAPTER IX

VITAMIN C

CHARLES GLEN KING

DIETARY PRACTICES AND SCURVY

The principle of preventing scurvy by the use of certain foods had to be learned repeatedly in early human experience Primitive peoples seldom had a choice of orange juice, grapefruit, tomato juice canta loupe or strawberries for breakfast, but nearly all tribal groups knew that fresh foods were necessary for their health and survival Practices varied from eating thistle tops in the Gobi Desert area to consuming water extracts of evergreen leaves in forested sections of North America Europe and Asia

Scurvy in the classic sense[1] is no longer a major disease but severe cases are encountered occasionally in nearly all medical centers and many mild cases remain undetected or are confused with mild cases of rickets There is good evidence that moderate deficiencies impair health without giving rise to the classic signs that result in a diagnosis of scurvy Therefore a reliable intake of vitamin C in foodstuffs consumed by persons in all age groups and in all economic brackets is an item of continuing interest and practical concern

Since the vitamin either as ascorbic acid or in the form of dehydroascorbic acid is easily destroyed in many foods during wilting crushing chopping cooking drying or simple storage vitamin C has served as a sensitive indicator of processing and storage losses in nutritive quality The vitamin is relatively stable in canned and frozen foods however when they are properly processed and stored Acidic foods (oranges, lemons grapefruit and tomatoes) and some foodstuffs that retain a living condition during storage (pota toes peppers cabbage turnips avocados and bananas) generally retain their vitamin C content fairly well.

1 Hess, A. F Scurvy Past and Present, Philadelphia, J B. Lippincott Company 1920

The age distribution of patients found to have scurvy in typical American communities shows a characteristic pattern of highest incidence during the 6 to 24 months of age period, with a much lower incidence among younger and older children. Most infants are born with a reserve of vitamin C in their tissues, so that a depletion period of a few months normally precedes the physical signs of scurvy. There is no convincing evidence, however, that infants have a special capacity to synthesize the vitamin, as has been suggested. If the infant is breast fed, there is practically no risk of a vitamin C deficiency. In contrast the feeding of cow's milk without a specific supplement involves a relatively high risk of vitamin C deficiency because the initial content is only about one third to one fourth of the quantity supplied in human milk, and this initial content is often reduced during processing and storage. Fresh cow's milk *normally will prevent* scurvy, but the risk (from infection) to health from unpasteurized milk is too great to justify its use regularly as an antiscorbutic food. It is possible to conserve most of the vitamin C in milk during commercial pasteurization and even during drying and sterilizing, but routine market supplies should not be relied on.

Elderly persons who live alone and use foods that can be purchased, stored and prepared in simple fashion *often use foods extremely low in vitamin C content*. Consequently, the colloquial terms "widow's scurvy," "bachelor's scurvy," and "old maid's scurvy" rival that of "infant scurvy" in usage.

DEPLETION OF BODY RESERVES

Many recent nutrition surveys in the United States and Canada have demonstrated an appreciable incidence of chronic vitamin C deficiency characterized by low intakes of antiscorbutic foods, varying degrees of tissue injury without signs of acute deficiency and low tissue storage as measured by low excretion levels and low concentrations in whole blood, white blood cells or blood plasma.[2]

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2 *Bessey, O. A., Lowry, O. H., and Brock, M. J.* A Quantitative Determination of Ascorbic Acid in Small Amounts of White Blood Cells and Platelets, J. Biol. Chem. **168**: 197, 1947. Linghorne, W. J., McIntosh, W. G., Tice, J. W., Tisdall, F. F., McCreary, J. F., Drake, T. G. H., *Greaves, A. V., and Johnstone, W. M.* The Relation of Ascorbic Acid Intake to Gingivitis, Canad. M. A. J. **54**: 106, 1946.

Controlled depletion experiments have demonstrated the following general sequence of changes

1 Decreased urinary excretion is evident within a few days and continues through a period of several weeks and months gradually approaching a zero level below which interfering substances make the analyses uncertain

2 A more gradual decrease in blood plasma concentration occurs from a saturation range of 1 to 2 mg per hundred ml to levels that are indicative of moderately low intake but with little risk of physical signs of deficiency (0.3 to 0 6 mg per hundred ml and, gradually to extremely low levels recorded as 0 to 0 3 mg per hundred ml There is considerable individual variation in the relationship between "zero plasma concentration and the duration of depletion

3 Continued low excretion and low tissue concentrations are followed by chemical and physical evidence of impaired function. The rate, as well as the duration, of depletion severely affects the nature of tissue changes [3]

There is inadequate evidence to permit satisfactory appraisal of the physiologic significance of the intermediate and lower levels of tissue storage There is reason to believe however on the basis of clinical observations and animal experimentation that health can be significantly impaired when the tissue concentration is low well in advance of physical changes associated with scurvy

ONSET OF SIGNS AND SYMPTOMS

Evidence of impairment to health is generally reflected by one or more of the following types of change altered tooth and bone structures (if examined microscopically—especially the odontoblasts fibroblasts and osteoblasts) decreased capacity to form and maintain a normal collagen level slow healing of wounds decreased capillary (or venule) strength as revealed by petechial hemorrhages when negative or positive pressure tests are applied decreased phosphatase esterase

3 Ya o sky M Almaden P., and King C. G The Vitamin C Content of Human Tissues, J Biol. Chem **106**: 5 5 1934 King C. G Musulin R K. and Swanson, W F Effects of Vitamin C Intake upon the Degree of Tooth Injury Produced by Diphtheria *Toxin, Am J Pub.* Health **30**: 1068, 1940 Kruse, H D A Concept of the Deficiency States, Milbank Memorial Fund Quart. **20**: 245 194.. The Gingival Manifestation of Avitaminosis C, id. **20**: 290 194.. Boyle, P E. Bessey O A and Wolbach, S B Experimental Alveolar Bone Atrophy Induced by Ascorbic Acid Deficiency and Its Relation to Pyorrhea Alveolaris, Proc. Soc. Exper Biol & Med. **38**: 33 1937 P ant, C. L. Bly C. G and Sutherland, K. The Mechanism, Course and Pathological Changes of Scorbutic Arthropathy Changes in the Guinea Pig, Report no. 61 Medical Nutrition Laboratory Chicago, 1949

and oxidase enzyme content of tissues, decreased capacity to metabolize the amino acids, tyrosine and phenylalanine, decreased capacity to combat infections, edema and reddening of the gums, tenderness to touch irritability, pain during movement, subcutaneous and subperiosteal hemorrhages, beading of ribs at the costochondral junctions, loss of appetite, loss of weight or failure to grow, muscular weakness, anemia, skin lesions, and fracture at epiphyses of long bones

Roentgen examination of the long bones also reveals characteristic changes that serve as an aid in diagnosis A band caused by increased density near the ends of the shaft is often referred to as the "scorbutic white line" The epiphyses show a characteristic halo' appearance Both changes result essentially from disorganized calcification Rarefaction often becomes evident on the shaft side of the hypercalcified area, and there is an increased risk of fracture along the zones of rarefaction Characteristic lesions of the periosteum do not become fully evident by roentgen examination until after therapy permits recalcification and partial healing The bone lesions caused by scurvy are frequently complicated by the simultaneous occurrence of rickets

Swelling at the ends of the long bones (but not actually in the joints) is frequently accompanied by subperiosteal hemorrhage before or *in* parallel with evidence of petechial hemorrhage and enlargement of the costochondral junctions The latter is not uncommonly confused with the beading caused by rickets The sharpness of the angle at the margin of beading is often indicative of scurvy but this characteristic cannot be relied on since it is in part dependent on previous fracture

The gum lesions are characterized by gingival swelling, tenderness bleeding and hyperemia Subsequent to swelling there may be a characteristic atrophy with resultant retraction of the gingiva Acute human or experimental animal deficiencies may produce no perceptible changes in the gums however and thus reliance on this symptom may lead to failure to identify scurvy

In experimental animals it has been demonstrated that during vitamin C depletion there is a progressive increase in oxygen consumption a lowered capacity to metabolize glucose a lowered capacity to synthesize

hormones of the adrenal cortex and spleen, an impairment of aromatic amino acid oxidation, a decrease in enzyme content of nearly all tissues, a lessened efficiency of calcium utilization and a lessened capacity to resist injuries caused by diphtheria toxin.

Recent work has demonstrated an intimate relation between vitamin C and the oxidative degradation of two amino acids, phenylalanine and tyrosine.[4] Clinical observations have indicated a similar relationship in infants as revealed by excretion of incompletely oxidized amino acids and consequent formation of melanin type pigments in the urine.

The decided decreases in activity of many specific oxidative and hydrolytic enzymes in the tissues of scorbutic animals makes it evident that chemical disturbances induced by vitamin C deficiency are exceedingly complex and involve reactions that are characteristic of all living cells.[5]

CAPILLARY FRAGILITY

Many investigations of vitamin C deficiency in man and in animals, including prompt and complete response when the pure vitamin is administered, demonstrate unmistakably that the hemorrhages and other tissue lesions characteristic of scurvy are specifically related to ascorbic acid. Studies of catechol, rutin, hesperidin chalcone and other nonspecific polyphenols that occur widely distributed in vegetables and fruits indicate that these materials, under specific experimental conditions, can exert a protective effect in regard to capillary strength. These compounds have not been established as essential nutrients, however, and hence should not on the basis of present evidence be classified as vitamins or confused with vitamin C nomenclature.

Dehydroascorbic acid, fed in dilute acid solution to guinea pigs, is almost as effective as the reduced form

4. Sealock, R. R., Galdston, M., and Steele, J. M.: Administration of Ascorbic Acid to an Alcaptonuric Patient, Proc. Soc. Exper. Biol. & Med. 44:580, 1940. Clegg, R. E., and Sealock, R. R.: The Metabolism of Dihydroxyphenylalanine by Guinea Pig Kidney Extracts, J. Biol. Chem. 179:1037, 1949. Woodruff, C. W., Cherrington, M. E., Stockwell, A. K., and Darby, W. J.: The Effect of Pteroylglutamic Acid and Related Compounds upon Tyrosine Metabolism in the Scorbutic Guinea Pig, J. Biol. Chem. 178:861, 1949.

5. Danielli, J. F., Fell, H. B., and Kodicek, E.: The Enzymes of Healing Wounds. II. The Effect of Different Degrees of Vitamin C Deficiency on the Phosphatase Activity in Experimental Wounds in the Guinea Pig, Brit. J. Exper. Path. 26:367, 1945. Harrer, C. J., and King, C. G.: Ascorbic Acid Deficiency and Enzyme Activity in Guinea Pig Tissues, J. Biol. Chem. 138:111, 1941. Murray, P. D. F., and Kodicek, E.: Bones, Muscle and Vitamin C, J. Anat. 83:158, 1949.

of the vitamin Conversion to the reduced form occurs rapidly, so that its role and dosage value are essentially identical with that of ascorbic acid The end products of ascorbic acid in vivo have not been well identified but in vitro experiments have shown that oxalic acid and *l* threonic acid constitute the two major products of oxidation

FUNCTIONAL ROLE

In vitro experiments have demonstrated that ascorbic acid is sensitive to reversible oxidation by a number of tissue catalysts including the cytochrome system, peroxidases ascorbic acid oxidase (in plants), poly phenol oxidases (in the presence of quinone carriers), hemochromogens and adrenochrome Reducing agents or systems that might act on dehydroascorbic acid and thus establish the vitamin as a significant respiratory carrier have been studied in several laboratories Sulf hydryl compounds including glutathione cysteine and HS-proteins have been most prominent as reducing agents The exact steps by which the vitamin functions in major degree as a tissue catalyst have not been well identified

In plant tissues the origin of ascorbic acid has been traced fairly definitely to glucose, but the intermediate steps have not been identified either in plants or in animals that have a capacity for synthesizing the vitamin The structural analogy to glucose is indicative that if the vitamin is derived without cleavage of the carbon chain there must be at least four intermediate steps (*a*) oxidation of carbon 6 to a carboxyl (*b*) oxidation of carbon 5 or carbon 4 to a ketone followed by enolization (*c*) reduction of carbon 1 to an alcohol and (*d*) lactonization

Synthesis of the vitamin in animal tissues as in the rat and in cattle can be accelerated greatly by feeding any one of a great variety of known organic compounds These substances are characterized broadly by their action both as nerve depressants and accelerators of glucuronic acid excretion Chlorobutanol and barbiturates are among the most active accelerating agents

RECOMMENDED INTAKE

During infancy and early childhood as soon as breast feeding has been discontinued provision should be made for a regular intake of vitamin C either in the milk

formula or in a specific supplement Ascorbic acid can be incorporated readily in powder or tablet form in formulas, and it is generally a simple matter to provide an adequate supply of vitamin C through the use of orange juice, grapefruit juice, tomato juice—and beyond infancy—cantaloupe, strawberries, lemon juice, bananas, green leafy foods (not overcooked) or green beans and peas

There are several approaches to the estimation of the level of vitamin C intake that should characterize good diets for persons in different age groups and different

Recommended Levels of Vitamin C Intake

	Ascorbic Acid (Mg Per Day)
Man (154 lb 70 Kg)	
Sedentary	5
Moderately active	75
Very active	75
Woman (123 lb., 56 Kg)	
Sedentary	70
Moderately active	0
Very active	70
Pregnancy (latter half)	100
Lactation	1[illegible]0
Children up to 12 years	
Under 1	30
1 3 (29 lb 13 Kg)	35
4-6 (42 lb 19 kg)	50
7-9 ([illegible] lb [illegible] kg)	60
10-12 (5 lb 34 kg)	75
Children over 12 years	
Girls 13-15 (108 lb 49 Kg)	80
Girls 16-20 (119 lb 54 kg)	80
Boys 13 15 (103 lb 47 kg)	90
Boys 16-20 (141 lb 64 kg)	100

environments For infants one has a valid measure of the natural (perhaps the optimal) intake as revealed in the composition of human milk A second approach is provided by noting the intake that is required to maintain tissue concentrations comparable to those found in experimental animals having a capacity to synthesize the vitamin and thus maintain a normal physiologic control of tissue concentration A third type of evidence is provided by studies with primates and guinea pigs the only experimental animals known to require vitamin C All other animals at least in the higher orders maintain the vitamin in their tissues by synthesis instead of being dependent on a nutrient

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specific action at the site of deposition Indirect evidence exists that vitamin D may act to aid conversion of organic phosphorus to inorganic phosphorus at the site of deposition in bone[6] Alkaline phosphatase may be a part of this picture Its function is not known except that it is related to phosphorus metabolism It can change organic phosphorus to inorganic phosphorus Its increase in the blood is one of the first evidences of vitamin D deficiency

Deficiency of vitamin D results in poor retention of calcium and phosphorus, which in turn may cause retarded skeletal growth In its more severe degrees it causes rickets in those who are still growing and osteomalacia in those fully grown In some circumstances it may result in tetany

The rate of skeletal growth is controlled in part by the availability of calcium and phosphorus for mineralization of bone The effect of vitamin D in regulating calcium and phosphorus metabolism and, therefore, on bone growth is particularly observable in infancy, when growth is rapid[7] Babies receiving only the minimum amount of vitamin D for rickets prevention have average linear growth Those who receive amounts of vitamin D that produce better calcium and phosphorus retention (300 to 400 units a day) grow at rates greater than average Amounts of vitamin D considerably in excess of the need cause loss of appetite, decreased intake of food and consequently, decreased total retention of calcium and phosphorus, babies with this condition grow at rates less than average

Another effect of vitamin D deficiency has been shown by Warkany[8] for animals It is doubtful that a

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6. Cohn W E and Greenberg D M Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes III The Influence of Vitamin D on the Phosphorus Metabolism of Rachitic Rats J Biol Chem **130**:675 (Oct) 1939 Greenberg D M Studies in Mineral Metabolism with the Aid of Artificial Radioactive Isotopes VIII Tracer Experiments with Radioactive Calcium and Strontium on the Mechanism of Vitamin D Action in Rachitic Rats J Biol Chem **157**:99 (Jan) 1945 Shimotori N, and Morgan A F Mechanism of Vitamin D Action in Dogs Shown by Radioactive Phosphorus, J Biol Chem **147**:201 (Jan) 1943

7 (a) Stearns G Jeans P C, and Vandecar V The Effect of Vitamin D on Linear Growth in Infancy J Pediat **9**:1 (July) 1936 (b) Jeans P C and Stearns G The Effect of Vitamin D on Linear Growth in Infancy The Effect of Intakes Above 1 800 U S P Units Daily J Pediat **13**:730 (Nov) 1938 (c) Slyker F Hamil B M Poole M W Cooley T B and Macy, I G Relationship Between Vitamin D Intake and Linear Growth in Infants Proc Soc Exper Biol & Med **37**:499 (Dec.) 1937

8 Warkany J Effect of Maternal Rachitogenic Diet on Skeletal Development of the Young Rat Am. J Dis. Child **66**:511 (Nov) 1943

similar effect occurs in man When the mother was fed a rachitogenic diet and deprived of vitamin D, nearly half of the young were born with congenital skeletal malformations In general the bones were curved and shortened

The question arises of whether a distinction between vitamin D_2 and vitamin D_3 is of practical interest in human physiology It is known that for the chick many times as much *vitamin D_2 as vitamin D_3* is required for prevention of rickets It is known also that vitamin D_3 is more effective for the turkey poult than is cod liver oil A distinction between the two varieties of vitamin D is of practical importance to the producer of poultry feeds Such evidence as exists for man is still somewhat contradictory Viosterol (D_2) has been found less effective than cod liver oil in prevention of dental caries in orphanage groups [9] Cod liver oil has been found to produce more rapid healing of rickets in babies than did viosterol [10] In neither study could the subjects be closely controlled In a closely controlled inpatient study [11] of normal infants no difference was found between the two varieties when they were given as vitamin D milk and when calcium and phosphorus retentions were used as the criteria. Differences failed to appear, whether the milk contained 400 or 135 units to the quart In another well controlled study Glaser and co-workers [12] found no difference in retentions between vitamin D_2 and vitamin D_3 in a group of prematurely born babies It seems logical to believe that if no differences are found in calcium and phosphorus retentions no differences exist for man between the two forms of the vitamin

REQUIREMENT OF NORMAL INFANTS

A full term breast fed baby receives in his food an amount of calcium and phosphorus just sufficient to provide for good growth Although the intake is minimum the proportions of several of the milk constituents are such as to permit good absorption of these

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9 McBeath E C. and Verlin, W A. Further Studies on the Role of Vitamin D in the Nutritional Control of Dental Caries, J Am. Dent. A. 29:1393 (Aug) 194

10 B nes, D J Kau her M and Munks, B Metabolic Studies on Rachitic Infants, Am. J Dis. Child. 71:6-2 (June) 1946.

11 J ans, P C and Stearns, G Unpublished data.

12 Glaser K. Parmlee A. H., and H ilman, W S Comparative Efficacy of Vitamin D Preparations in Prophylactic Treatment of Premature Infants, Am. J Dis. Child. 77:1 (Jan.) 1949

minerals Also, if vitamin D is being given to the mother, the baby may receive up to 40 or more units daily in the milk It is because of these several factors that rickets is less common in breast fed than in artificially fed babies even when no vitamin D is given Nevertheless, rickets develops in some breast fed babies, and in any case more calcium and phosphorus are retained when vitamin D is given The requirement of the breast-fed baby is no greater and it may be less than that of the artificially fed baby

When babies are fed customary formulas of cow s milk, they receive ample amounts of calcium and phosphorus However the proportions of other constituents are such as to interfere with absorption of these minerals unless vitamin D is given When no vitamin D is given, the range of calcium retention is wide but the average is approximately 10 per cent of the intake When babies are given 90 to 100 units daily (the amount obtained by young babies in vitamin D milk containing 135 units to the quart), retention is increased to 25 to 30 per cent of the intake and the range of retention values is decreased, rickets is prevented and linear growth is average With 300 to 400 units daily as cod liver oil or milk containing vitamin D calcium retention is increased to between 35 and 40 per cent of the intake the range of retention values is further decreased and linear growth is greater than average Increase of the amount of vitamin D above 400 units has no effect in increasing the percentage of intake retained[13]

When 800 units of vitamin D are given daily the effect on retention and growth is identical with that of 300 to 400 units As the amount of vitamin D is increased further the percentage of calcium intake retained remains the same but with amounts of 1 800 or more units daily appetite is decreased after several months food intake is smaller and consequently the total calcium retention is less Linear growth then becomes retarded[7b] Thus mildly toxic effects occur with what is commonly prescribed and considered a reasonable and harmless prophylactic dosage

13 Houet R Metabolism of Vitamin D III Determination of Daily Need of the Vitamin in Babies Ann paed t. **167** 225 (Nov) 1946 Stearns G and Jeans P C The Effect of the Quantity of Vitamin D Intake on Calcium Retention in Infancy in Proceedings of the American Society of Biological Chemists, J Biol Chem. **114**: c (May) 1936

Some evidence exists that concentrates of vitamin D in solution in oil are not so well utilized by infants as are *the more dispersed forms* The concentration present in cod liver oil allows good utilization [14]

Rickets prevention by the administration of a single massive dose of vitamin D has had a number of advocates The practice had its start in Germany The earliest reports in this country were those of Zelson [15] Wolf [16] and Rambar and co-workers [17] although Vollmer [18] previously had reported such practice in the treatment of rickets The dose most commonly used is *500 000* to *600 000 units given either orally or* parenterally The antirachitic effect lasts about four months in nonrachitic infants [19] and two to three or more months in rachitic infants [20] Thus rickets can be prevented by giving 600 000 units three times a year Claim has been made that vitamin D in this amount is harmless Palmen [1] gave 500 000 units of vitamin D_2 to *7* nonviable newborn infants Subsequent examination showed no changes in the kidneys adrenals liver spleen, aorta or heart He gave the same massive single dose to 200 prematurely born infants without producing any clinically demonstrable injury Krestin [2]

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14 Lewis J M Clinical Experience with Crystalline Vitamin D *The Influence of the Menstruum on the Effectiveness of the Antirachitic* Factor J Pediat. **6**: 362 (March) 1935 Erben F Ueber den Einfluss des Losungsmittels auf die therapeutische Wirksamkeit des bestrahlten Ergosterin Munchen. med. Wchnschr **82**: 1 94 (Nov 8) 1935 Lewis J M Further Observations on the Comparative Antirachitic Value of Crystalline Vitamin D Administered in Milk, Corn Oil, or in Propylene Glycol J Pediat. **8**: 308 (March) 1936 Shelling D H Calcium and Phosphorus Studies XIII The Effect of Emulsification on the Potency of Viosterol in the Treatment of Rickets in Children J Pediat **10** 748 (June) 1937 Lewis J M The Influence of the Menstruum on the Effectiveness of Vitamin D Obtained from the Livers of the Percomorph Order of Fish J Pediat. **14**: 559 (May) 1939

15 Zelson C Prevention of Rickets in Premature Infants with Parenteral Administration of Single Massive Doses of Vitamin D J Pediat **17**: 73 (July) 1940

16 Wolf I J *Prevention of Rickets with Single Massive Doses* of Vitamin D J Pediat. **22**: 396 (April) 1943 Safety of Large Doses of Vitamin D in the Prevention and Treatment of Rickets in Infancy ibid **22**: 707 (June) 1943

17 Rambar A C. Hardy M and Fishbein, W I Hematologic and Radiologic Study of Infants Receiving Massive Doses of Vitamin D in Rickets Prophylaxis, J Pediat. **23**: 31 (July) 1943

18 Vollmer H J Treatment of Rickets and Tetany with a Single Massive *Dose* of *Vitamin D J Pediat.* **14**: *491* (April) 1939 Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D ibid. **16**: 419 (April) 1940

19 Huet R. Study of Vitamin D Storage in the Infant, Bull. Soc. chim. biol. **29**: 306 (Jan. March) 1947

20 Hottinger, R Calcium and Phosphorus Metabolism in Children IV Duration of Action of a Single Dose of 15 Mg of Vitamin D in a Rachitic Infant, Ann. paediat **107**: 35 (Nov) 1946

21 Palmén K Histologic Effect of Single Massive Doses of Vitamin D in Nonviable Infants, Nord. med. 30 [illegible] (April 1?) 1946.

22 Krestin D Prophylaxis of Rickets by Single Massive Doses of Vitamin D Brit. M. J 1: 8 (Jan. 20) 1945

gave 300,000 units orally to 93 infants under 2 years of age during the winter months, of these 90 remained free from rickets Jelke [23] reported prophylactic administration to a 9 month old baby of four doses of 500,000 units each at two month intervals Anorexia was noted after the second dose and greater anorexia after the third dose The anorexia lasted two weeks No physical damage was found

Houet [24] has reported balance studies of 5 normal and 4 rachitic infants after they had received 15 mg of vitamin D either orally or parenterally In general, the calcium retentions of the healthy infants remained relatively unchanged as a result of the medication The phosphorus retentions decreased in 3 of the 5 normal babies and remained at a lower level throughout the period of observation which was short. These studies seem to show that there is no immediate ill effect from the prophylactic use of 15 mg of either vitamin D_2 or D_3 The studies probably are not conclusive It appears true that deleterious effect, if any occurs, is moderate and curable More data covering a longer period, are needed to determine the advisability of this method of prophylaxis Does anorexia resulting in intake lowered enough to affect retentions and growth subsequently develop in babies treated in this manner?

The general consensus has been that the requirement of the prematurely born baby for vitamin D is greater than that of the baby born at term, yet no evidence for the opinion exists It is known that babies born prematurely develop rickets more often than those born at term but the difficulty lies in a deficiency of calcium and phosphorus rather than in an increased need for vitamin D [25] In fetal life the bones are mineralized during the last three months A baby born one month prematurely has only about half the amount of calcium he would have if he had been carried to term Thus the prematurely born

23 Jelke, H Vitamin D Poisoning Svenska lak tidning **43** 1372 (May 24) 1946

24 Houet, R Metabolism of Calcium and Phosphorus in Infancy II Effects of Oral Administration of 15 Mg Vitamin D on Phosphorus and Calcium Balance of the Infant, Ann paediat, **166** 177 (April) 1946 III Effects of Intramuscular Injection of 15 Mg of Vitamin D on the Utilization of Calcium and Phosphorus by the Infant, ibid, **167** 128 (Sept.) 1946

25 Stearns G Mineral Metabolism of Normal Infants Physiol Rev **19** 415 (July) 1939 Benjamin H R, Gordon, H H and Marples E. Calcium and Phosphorus Requirements of Premature Infants Am. J Dis Child. **65**: 412 (March) 1934

baby starts postnatal life with a large handicap in bone mineralization Furthermore, he has a small capacity for food, whereas the need for food is relatively great if growth expectations are to be met. While human milk contains enough calcium and phosphorus to supply the needs of the baby born at term, the amount is inadequate for the prematurely born baby Administration of vitamin D will not make up for this deficit in mineral Davidson and Merritt[26] found rickets in premature babies who had received large amounts of vitamin D If human milk is used it must be fortified with dried skimmed milk, or some special provision must be made to supply the increased need When the calcium and phosphorus requirement is supplied the need of the prematurely born baby for vitamin D is the same as that of the baby born at term This concept was confirmed by Glaser and co-workers[12] who found that doses of 100 and 800 units of each of four preparations of vitamin D were effective in preventing rickets and permitting normal growth They found as good calcium retention with 200 units of vitamin D as with 400 or 800 units They found also that vitamin D_2 gave the same results as vitamin D_3

REQUIREMENT OF CHILDREN

The fact that children past infancy need vitamin D is often overlooked A few children have good utilization of calcium and phosphorus without additional vitamin D but there is no simple way of recognizing such children For this reason it is appropriate for all children to have a vitamin D supplement. The need of the child for vitamin D has been shown by the observation of retentions of calcium and phosphorus with and without the vitamin Also Follis and co-workers[27] found histologic evidence of rickets in nearly half the children from 2 to 14 years of age seen at autopsy in a Baltimore hospital in these instances the relative roles of vitamin D deficiency and mineral deficiency are not too clear Again it is to be emphasized that intake of vitamin D will not compensate for a low calcium intake.

26 Davidson L. T and Merritt, K. K. Viosterol in the Prophylaxis of Rickets in Premature Infants Am. J Dis. Child. 48: 81 (Aug) 1934

27 Follis, R H Jackson D Eliot, M M., and Park, E. A. Prevalence of Rickets in Children Between Two and Fourteen Years of Age, Am. J Dis. Child. 66: 1 (July) 1943

The requirement of children for vitamin D has not had as much detailed study as has that of infants However, it is known that 300 to 400 units daily permits satisfactory calcium and phosphorus retentions when the diet contains appropriate and recommended amounts of these minerals [8]

During the prepubertal growth acceleration period and during adolescence the need for vitamin D is more universal than it is for the younger child past infancy During this period there is also a need for a greater intake of calcium than previously With an intake of recommended amounts of calcium and phosphorus, 400 units of vitamin D permits good retention of these minerals if the nutrition of the child is otherwise satisfactory Children who have had poor diets often fail to have good retention of calcium and phosphorus when first given a good diet After several months of a good diet retentions gradually increase to the expected level without increase in vitamin D above 400 units daily

REQUIREMENT OF ADULTS

After growth has ceased the need for vitamin D is minimum except during lactation and the latter part of pregnancy McKay and co-workers,[29] in a study of young women with a well selected diet, found that the addition of 500 units of vitamin D daily had little influence on calcium retention, in comparison with the same diet without supplemental vitamin D Other evidence indicates that vigorous adults leading a normal life have little need for vitamin D However it is believed desirable that small amounts be given to those whose habits shield them from sunlight Osteoporosis is common in the elderly Several possible causes have been postulated and perhaps the causes are multiple Until the cause is more definitely determined a small amount of vitamin D seems indicated

During lactation and the latter part of pregnancy the need for calcium and phosphorus is greatly increased During these periods supplemental vitamin D increases utilization The optimum amount is

28 Jeans P C and Stearns G The Human Requirement of Vitamin D J A M A 111 703 (Aug 20) 1938.
29 McKay H Patton M B Pittman M S Stearns G and Edelblute N The Effect of Vitamin D on Calcium Retentions J Nutrition 26 153 (Aug) 1943

not known, but the calcium and phosphorus retention values observed with a high vitamin D intake are no greater than those observed with a moderate intake From available evidence it seems likely that 400 units daily is adequate

VITAMIN D THERAPY

The chief therapeutic use of vitamin D is in the treatment of rickets Because of widespread prophylaxis clinically detectable rickets is relatively uncommon in this country Deficiency of vitamin D of a degree sufficient to cause rickets produces characteristic values for the amounts of calcium, phosphorus and phosphatase in the blood in the blood serum the amount of calcium is normal or slightly lowered the amount of inorganic phosphorus is much decreased, and the amount of phosphatase is increased The rachitic changes in bone are caused chiefly by the decrease in inorganic phosphorus and the disproportion between the calcium and phosphorus available An early effect of vitamin D therapy is an increase in serum phosphorus This increase is followed by mineral deposition in bone and eventual healing of the rachitic changes if vitamin D therapy is continued The amount of phosphatase decreases soon after treatment is started but it remains moderately elevated until healing is advanced and is the last of the blood values to become normal

An amount of vitamin D that will just prevent rickets will also cause healing but the process is much slower than if larger amounts are given Amounts recommended for treatment vary widely One thousand units daily will produce normal calcium and phosphorus values in the blood in approximately ten days and healing changes in the bones detectable by roentgenograms in about three weeks One thousand units daily is the minimum recommended therapeutic dose.[30] Three to four thousand units daily is often prescribed, and with this amount healing is more rapid In most instances no need exists for a larger amount or for more rapid healing of rickets The amount of vitamin D should be reduced to normal prophylactic dosage as soon as the rickets is under control

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30. Park E. A. The Therapy of Rickets, J. A. M. A. 115:370 (Aug 3) 1940.

Single massive doses, for example 600 000 units, have been used for treatment, with favorable results reported[31] Such treatment is justifiable only when circumstances are unfavorable for daily ingestion of more moderate doses Healing of rickets seems to be no more rapid with the massive dose than with the daily moderate dose

In the preceding discussion it is stated that an early effect of vitamin D therapy of rickets is an increase in serum phosphorus and deposition of mineral in bone Early in this course a lowering of the calcium content of the blood occurs, but this decrease is transitory and unimportant if vitamin D therapy is continued However, if the initial amount of vitamin D is minimum and its administration is stopped early, the blood calcium may decrease to a low level resulting in tetany As far as vitamin D is concerned the treatment of rachitic tetany is the same as that for rickets During the period of approximately ten days required for restoring calcium and phosphorus values in the blood to normal, other measures of control of the symptoms of tetany are indicated These may include intramuscular administration of magnesium sulfate or oral administration of calcium chloride or both

Clinically recognizable rickets from vitamin D deficiency after infancy is most uncommon in this country If it should occur the treatment is the same as that for infantile rickets Advanced and easily recognizable rickets occurs in childhood from other causes One such cause is chronic nephritis with failure of phosphorus excretion and usually subsequent resulting changes in calcium metabolism Another cause is the Fanconi syndrome in which the primary lesion appears to be in the function of the kidney tubules, because of which several materials are abnormally excreted in the urine, including increased amounts of phosphorus In these cases inorganic phosphorus in the serum is low Vitamin D therapy will cure neither of the preceding conditions

Another type of rickets is known as resistant rickets It is characterized by a low level of serum phosphorus for which no satisfactory explanation has been found

31 Krestin, D Treatment of Rickets with Single Massive Doses of Vitamin D_2, Lancet 248:781 (June 23) 1945

In the treatment of this type of rickets vitamin D is most useful but not when given in amounts customary for the treatment of rickets of vitamin D deficiency In order to provide beneficial results the doses of vitamin D must be large, often so large that close observation is required to prevent serious toxic effects The amount required varies with the child the range being commonly 50 000 to 500 000 units daily The finding of the proper dose is a trial and error procedure and often the requirement seems not to remain constant

Vitamin D is sometimes used in the treatment of hypoparathyroidism Perhaps more often dihydrotachysterol, a related product, is used for this purpose although vitamin D_2 and probably vitamin D_3 also, has identical effects in the treatment of this condition The doses required are large, and close observation of the level of calcium in the serum is required The daily *amount required for maintenance varies from person to person* but usually is in the range of 0 6 to 1 0 mg of dihydrotachysterol or 3 to 5 mg (133 000 to 200 000 units) of vitamin D This type of treatment usually is initiated with amounts at least three times as large as the maintenance dose the amount is decreased to maintenance dose when the level of calcium in the serum reaches normal The action of the parathyroid hormone is different from that of vitamin D in customary prophylactic amounts The hormone acts to maintain normal calcium values in the serum and at the same time decreases resorption of phosphorus by the kidneys Vitamin D in moderate amount acts to maintain normal inorganic phosphorus values in the serum and increases resorption of phosphorus by the kidneys However vitamin D increases the calcium level in plasma when toxic doses are given Both substances when vitamin D is given in large amounts remove calcium and its associated minerals from the stores in bone.

Several patients with other diseases have been reported as being benefited by massive doses of vitamin D These include patients with chronic arthritis psoriasis pemphigus and allergic conditions These reported good results have not been confirmed adequately and it is believed that the evidence does not warrant the claim that vitamin D is beneficial.

HYPERVITAMINOSIS D

Massive doses of vitamin D have been given to persons of various ages for various reasons, particularly in the treatment of chronic arthritis. In some reported instances large doses have been given to infants, sometimes through error on the part of the mother. Many instances of the toxic effects of large amounts have been recorded. The amount that is toxic varies in different persons and even at different times in the same person. Some adults show symptoms of toxicity with 150,000 units daily or even less.[32]

Several symptoms and findings are common to most cases of intoxication. Frequent among the early symptoms are anorexia, thirst, lassitude and urinary urgency with or without polyuria. Later symptoms include nausea, vomiting, diarrhea and abdominal discomfort. The increased excretion of calcium in the urine may cause calcium deposits in the kidneys with resulting kidney damage and decreased renal function. Anorexia, nausea and vomiting lead to weight loss and subsequent debility, and damaged cells in various organs, arteries and arterioles become the repository for calcium salts. While these changes usually accompany hypercalcemia and hyperphosphatemia, it has been shown in dogs that metastatic calcification can occur without increase in the level of calcium in the blood.[33] If hypervitaminosis continues the various changes lead to death.

An additional finding in the hypervitaminosis D of infants and growing children is a dense deposition of mineral in the zone of provisional calcification in the metaphyses of long bones. This deposition is made at the expense of the diaphysis.

Vitamin D is stored in the body, and the effects of excessive dosage may be expected to be cumulative. Frost and co-workers[32a] reported continued hypercalcemia, high urinary excretion of calcium and persistence of renal damage eight months after stopping treatment with 125 000 units of vitamin D daily.

32 (*a*) Frost, J. W., Sunderman, F. W., and Leopold, I. S.: Prolonged Hypercalcemia and Metastatic Calcification of the Sclera Following the Use of Vitamin D in the Treatment of Rheumatoid Arthritis. Am. J. M. Sc. **214**: 639 (Dec.) 1947. (*b*) Covey, C. W., and Whitlock, H. H.: Intoxication Resulting from Administration of Massive Doses of Vitamin D with Report of 5 Cases. Ann. Int. Med. **25**: 508 (Sept.) 1946.

33 Bauer, J. M., and Freyberg, R. H.: Vitamin D Intoxication with Metastatic Calcification. J.A.M.A. **130**: 1208 (Apr. 27) 1946.

CHAPTER XI

FAT-SOLUBLE VITAMINS A, E AND K

HUGH R. BUTT

VITAMIN A

Chemistry—Vitamin A is a colorless, fat-soluble vitamin Karrer and associates isolated it in 1931 and determined its structure but effective syntheses of vitamin A were achieved by Milas[1] and others only during the last five years

The vitamin is an alcohol and hence is not itself saponifiable Evidence has been presented indicating that vitamin A occurs in more than one form The form that predominates in the tissues of salt water fish and mammals has been designated as vitamin A_1 and the form which predominates in the tissues of fresh water fishes as vitamin A_2 Both forms appear to exert similar functions, although vitamin A_1 is considerably more effective in mammals than vitamin A_2

The international unit of vitamin A has been fixed as the activity of 0 6 micrograms of pure beta-carotene This dissolved in a vegetable oil at such concentration that 1 Gm contains 0 3 mg of beta-carotene constitutes the international standard preparation of vitamin A One international unit of vitamin A is contained therefore in every 2 mg of the international standard preparation

Vitamin A is fairly stable to heat is not appreciably soluble in water and is destroyed by oxidation The structural formula of vitamin A is shown in figure 1

During early experimental work on the promotion of growth it soon became evident that some relationship existed between the fat soluble vitamin A and the presence of plant pigments but it was not until 1930 that it was generally realized that carotene possessed growth-promoting activity It is known now that much of the

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1 Milas, N A Synthesis of Biologically Active Vitamin A Substances, Science 103:581 (May 10) 1946.

vitamin A man receives from his food occurs in the form of its precursors the yellow and red carotenoid pigments (provitamins)

These provitamins, called ' carotenoids," are extremely sensitive to oxidation and light but are quite stable to heat. Little is known of their biogenesis, and none have been synthesized The beta form is apparently the most active precursor, and its activity seems to depend on the presence of the beta ionone ring

Although its exact function is unknown, carotene is important in the physiologic processes of plants It is associated closely with chlorophyll although it is not lost when chlorophyll disappears at the time of the yel lowing of the leaves However, it has been destroyed completely by the time the leaves are dry and dead

Sources —Vitamin A is present only in the animal organism Fish liver oils are the richest source, but

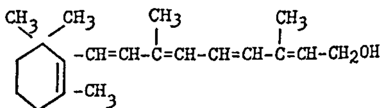


Fig 1 —The structural formula of vitamin A

milk butter margarine fortified with vitamin A and egg yolks are also rich sources Human milk is a good source of vitamin A and carotene The colostrum from the human breast has from two to three times as much biologic vitamin A activity as milk secreted soon after parturition and this human milk has from five to ten times the biologic vitamin A activity of cow's milk One can increase the content by giving supplementary vitamin A to the mother [2] but from data at hand it seems that the best method of vitamin A therapy when the object is to give the child a reserve of the vitamin is to give it directly

Because of its chemical properties foods which are heated for long periods of time lose an appreciable

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2 Hrubetz, M C Deuel H J Jr and Hanley B J Studies on Carotenoid Metabolism V The Effect of a High Vitamin A Intake on the Composition of Human Milk J Nutrition 29 245 (April) 1945
Clements, F W Manifestations of Nutritional Deficiency in Infants in Harris, R S and Thimann, K V Vitamins and Hormones Advances in Research and Application New York, Academic Press, Inc., 1946, vol. 4, pp 71 133

amount of vitamin A Boiling, canning or freezing foods does not cause loss of the vitamin, but drying and dehydration cause considerable loss

Among the best sources of provitamin A are thin green leaves The exact relationship between the degree of greenness and the content of the provitamin is not understood but it is well known that the outer green leaves of iceberg lettuce or cabbage are much more potent in provitamin A than are the inner leaves Peas, green beans, green peppers asparagus and green celery are examples of vegetables known to have a high content of carotene Yellow fruits and vegetables such as carrots sweet potatoes apricots yellow peaches and yellow tomatoes are other examples of rich sources of carotene Nuts and cereal grains, with the exception of those having considerable green or yellow color are poor sources Yellow corn is the most important source of carotene in this group

Requirements —The minimal requirement for vitamin A in man is still unknown, but in many animals the amount needed has been found to be related to body weight[3] In practice the vitamin A needs of the human body are usually taken care of by the mixture of vitamin A and provitamin A present in the diet It is difficult to calculate the precise vitamin A value of individual precursors for the simple reason that the precursors do not always yield their theoretic vitamin A values Dr Lela Booher and her co-workers[4] in a study of beta-carotene and vitamin A requirements observed that it took on an average, 73 per cent more of beta carotene (in oil) than vitamin A as it occurred in cod liver oil to maintain normal dark adaptation after vitamin A depletion It is apparent from these and other reports that the human being utilizes vitamin A from various sources with differing degrees of efficiency Until more is known about the factors surrounding the utilization of provitamin A the precise method of calculating the vitamin A values of ordinary diets will not be known However it is probably safe to assume that

3 Guilbert H R, Howell C. E. and Hart, G H Minimum Vitamin A and Carotene Requirements of Mammalian Species, J Nutrition 19:91 (Jan.) 1940

4 Booher L. E. Callison E. C. and Hewston, E. M Experimental Determination of Minimum Vitamin A Requirements of Normal Adults, J Nutrition 17:317 1939 Booher L. E. and Callison, E. C. Minimum Vitamin A Requirements of Normal Adult Utilization of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure J Nutrition 18:459 1939

such vegetables as carrots, which are rich in carotene, can be relied on as important sources of vitamin A, even though it may take as much as 4 parts of carotene to supply 1 part of vitamin A As was pointed out in the 1948 revision of the Food and Nutrition Board's Table of Recommended Dietary Allowances,"[5] it is currently considered that the requirement for vitamin A is from 25 to 55 international units per kilogram of body weight, or 2 000 to 4,000 units of vitamin A per day for the adult, and "twice these amounts or more if the sole source is carotene from foods' The Food and

Table of Recommended Daily Dietary Allowances of Vitamin A

	Vitamin A (I U per Day)
Normal adults	5 000
Pregnancy (latter half)	6,000
Lactation	8,000
Children	
Under 1 year	1,500
1 3	2,000
4-6	2,500
7 9	3,500
10-12	4,500
13-15	5,000
Boys 16-20 years	6 000

The allowances as given here are based on the premise that approximately two thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A.

Nutrition Board's recommended daily dietary allowance of vitamin A is given in the accompanying table

Absorption —Vitamin A Since vitamin A is a fat soluble compound its absorption may be facilitated by the simultaneous absorption of a certain amount of fat, but there is not universal agreement on this point[6] Most workers feel that the presence of bile is not necessary for proper absorption of the vitamin Absorption of vitamin A reaches its maximum three to five hours after administration

5 Recommended Dietary Allowances Revised 1948 National Research Council Food and Nutrition Board no 129 1948

6 Ingelfinger F J Moss R E and Helm J D Jr The Effect of Atropine Upon the Absorption of Vitamin A, J Clin. Investigation 22 : 699 (Sept) 1943

Although apparently some vitamin A is lost in feces, nothing is known of the degree of destruction of the vitamin in the gastrointestinal tract under either normal or pathologic conditions In a case of fistula of the thoracic duct studies made after administration of vitamin A or carotene by mouth revealed that little carotene passed through the chylous fluid whereas nearly all the vitamin A could be recovered from it [7]

In patients with sprue treated with pteroylglutamic acid Fox [8] and Darby and co workers [9] have shown that serum levels of vitamin A are increased thus indicating that the function of the intestinal tract and perhaps its ability to absorb vitamin A are affected It has been further demonstrated by Weick and Tsao [10] and Danielson and co-workers [11] that the serum level of vitamin A can be increased both in normal children and in children with cystic fibrosis of the pancreas by the administration of vitamin A to which emulsifiers have been added This preparation seems to give the best results, but caution must be exercised until the safety of the emulsifying agent used has been demonstrated

Carotene Carotene is absorbed less rapidly than vitamin A and its absorption is subject to several more hazards Proper absorption of carotene requires the presence of bile in the intestinal tract and in those conditions in which bile is excluded completely or partially from the intestinal tract or in those instances in which bile salts of good quality are poorly excreted, bile must be given as a supplement in order to insure proper absorption Chronic diarrhea, pancreatic dysfunction celiac disease or sprue also may inhibit absorption of carotene As with vitamin A a certain amount of normal absorption of fat also seems necessary for proper transportation of carotene across the intestinal wall It has been shown that liquid petrolatum may inhibit seriously the absorption of carotene

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7 Forbes, G B Chylothorax in Infancy Observations on the Absorption of Vitamins A and D and on the Intravenous Replacement of Aspirated Chyle J Pediat. 25:191 (Sept.) 1944

8. Fox, H J Absorption of Unemulsified and Emulsified Vitamin A in Sprue, J Lab. & Clin. Med. 34:1140 (Aug) 1949

9 Darby W J Kaser, M M., and Jones, E. Influence of Pteroylglutamic Acid (Member of Vitamin M Group) on Absorption and Storage in the Liver of the Rat J Nutrition 33:[illegible]41 (Jan.) 1947

10 Weick, C and Tsao, M Comparison of Absorption in Normal Children and Children with Cystic Fibrosis of the Pancreas Using Oily and Water Soluble Preparations, Univ Hosp. Bul. Ann Arbor 13:114 (Nov) 1947

11 Danielson, W H Palmer H. D., and Binkley E. L. Absorption of Different Forms of Vitamin A in Cystic Fibrosis of Pancreas, Rocky Mountain M. J 44:6[illegible]6 (Aug) 1947

Maximal concentration of carotene in the blood is reached in seven to eight hours after administration and the fecal excretion accounts for only a small portion of the unutilized excess The rest apparently finds other channels of excretion or is destroyed in the intestine or elsewhere Under normal conditions the kidney apparently plays no part in the disposition of either vitamin A or its precursors

Storage—The capacity to store vitamin A varies widely in different species of animals The rat has a large capacity for the storage of vitamin A, whereas the rabbit and guinea pig retain little, even when ingesting diets rich in carotene It has been shown that maximum storage of vitamin A in the livers of rats occurs when the vitamin is administered orally rather than parenterally, subcutaneously or intramuscularly[12] Rodahl[13] reported recently that polar bears seem to be capable of storing huge amounts of vitamin A in their livers He found 26 700 and 21 900 international units of vitamin A per gram respectively in two specimens of the wet material In fish more vitamin A is deposited in the tunica propria of the mucosa of the intestine than in the liver

In human beings the liver probably stores about 95 per cent of the vitamin A reserve of the body As a rule the amount stored in the liver is least at birth and during childhood, irrespective of the diet of the mother and increases gradually with advancing age Examinations of the livers of healthy persons who died suddenly from accidental causes have shown the average vitamin A content of the liver to be between 200 and 400 international units of vitamin A per gram The amount of vitamin A stored in the liver in instances of hypervitaminosis A had not been reported up to the time of writing The exact mechanism by which vitamin A is called forth from reserve storage is not known

Hypervitaminosis A—If large amounts of vegetables rich in carotene are ingested by normal persons or persons suffering from certain diseases such as diabetes carotene may accumulate in the skin in amounts sufficiently large to cause a deep yellow color The condition

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12 Lemley J M Brown, R A Bird O D and Emmet, A. D Absorption and Storage of Vitamin A in the Liver of the Rat J Nutrition 33 53 (Jan) 1947

13 Rodahl K. Toxicity of Polar Bear Liver Nature **164**: 530 (Sept 24) 1949

is known as carotenosis and is harmless The yellow color tends to disappear quite promptly on reduction of the carotene intake.

As yet, there is no evidence of toxic effect occurring in foods, although it is interesting to note that Eskimos consider the livers of the polar bear and the Greenland fox as poisonous The livers are reported to contain about 25 000 and 12 000 international units respectively of vitamin A per gram [14]

In 1944 Josephs [15] published a report of hypervitaminosis A in a 3 year old boy Some two years later Toomey and Morissette [14] reported a case in a 23 month old infant. Since that time the condition has been observed and reported from other clinics [16] The condition seems to be due to the regular ingestion of large doses of vitamin A concentrates over a long period Recovery tends to follow the withdrawal of vitamin A supplements

In summarizing the study of his case, Toomey reported the following conditions hepatomegaly without splenomegaly increased levels of vitamin A in the serum, increased levels of serum lipids abnormalities of bones increased levels of serum phosphate, low levels of serum proteins sparse coarse hair, avid appetite for butter abnormal intake of vitamin A pain and localized periosteal swellings recovery from pain when vitamin A is withheld and prompt recovery after exclusion of vitamin A from the diet

There is no danger of the development of hypervitaminosis A except when excessively large doses of the concentrate have been ingested over long periods There is a wide zone of safety between the prophylactic and the dangerous doses of vitamin A

(An extensive discussion of vitamin A deficiency appears in chapter 21)

VITAMIN E

Chemistry—In 1925 Evans and co-workers [17] and Matill demonstrated that vitamin E must be included

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14 Toomey J A., and Morissette R. A. Hypervitaminosis A, Am. J Dis. Child. 73:4 3 (Ap 1) 1947

15 Josephs, H W Hypervitaminosis A and Carotenemia, Am. J Dis. Child. 67:33 (Jan.) 1944

16. Rothman, P A. and Leon E. E. Hypervitaminosis A R diology 51:368 (Sept.) 1948 Wyatt, T C Carabelo, C. N., and Fletcher M E. Hypervitaminosis A Report of a Case to be published. Caffey J Poisoning Due to Excess Vitamin A It Relation to Infantile Cortical Hyperostosis, Am. J Dis. Child. 79:404 (Feb.) 1 50

17 Evans H M and Burr G O The Anti-Sterility Vitamin Fat Soluble E, Proc. Nat. Acad. Sc. 11:334 19 5

in the diet of the rat to insure successful reproduction Vitamin E activity is exhibited by at least three naturally occurring compounds They are alpha, beta and gamma-tocopherol All these are fat-soluble substances that are only slightly soluble in water They are stable at high temperatures (200 C) but rapidly lose their activity in the presence of ultraviolet rays or mild oxidizing agents

Because the three tocopherols which have been demonstrated to have vitamin E activity are so closely related they are all referred to as vitamin E Synthetic racemic tocopherol acetate in olive oil is the international standard preparation of vitamin E The international unit is the vitamin E activity of 1 0 mg of the standard preparation This quantity represents the average amount of the substance which prevents resorption of the fetus when administered to rats deprived of vitamin E

Vitamins E and their esters are easily absorbed from the intestinal tract These vitamins are stored in small amounts in body fats muscles and the anterior lobe of the pituitary gland Although they are fat soluble they are not distributed according to this chemical property Tissue of the heart and lungs although it contains relatively small amounts of fat may contain more of the vitamin E than body fat and much more than the liver[18]

Sources—The animal organism contains only small amounts of vitamin E and finds its richest supply in plant materials particularly in vegetable oils and green leaves Wheat germ oil is the richest natural source of vitamin E but the vitamin is also found in considerable quantities in lettuce oil rice germ oil cottonseed oil and other seed grain oils Synthetic tocopherols are also available commercially

Requirements Practically nothing is known concerning the requirement of man for vitamin E Comparatively few clinical studies dealing with the role of vitamin E in human physiology have been made and thus far they have not led to definite conclusions There seems to be agreement that vitamin E is of no value in the treatment of sterility in man In fact it is not known whether or not manifestations of a real deficiency of the vitamin have ever been observed in man

18 Mason K E Distribution of Vitamin E in the Tissues of the Rat, J Nutrition 23 71 (Jan) 1942

Physiologic Aspects—Reproductive System The effect on the rat of deprivation of vitamin E is well known In the male it produces irreversible sterility characterized by degeneration of the germinal epithelium, in the female it has been shown that although gestation starts normally after conception in moderate deficiency gestation may be prolonged with the fetus born dead or the newborn rat dying in the postpartum period When there is a pronounced deficiency of vitamin E the fetus may begin to develop normally but later degenerates and dies and may even undergo complete resorption These observations led to the use of the terms antisterility vitamin" and reproductive vitamin' Since these terms are not applicable to human nutrition it is probable that their use should be abandoned

Muscle Metabolism In 1928 Evans and Burr[19] first called attention to the muscular paralysis which developed in the suckling rats of mothers who had a deficiency of vitamin E Since then lesions have been demonstrated in the muscles of rabbits ducklings young guinea pigs hamsters and older rats on diets deficient in vitamin E These lesions may be prevented or cured by the use of tocopherol

Antioxidant Activity Perhaps the most striking chemical property of the vitamins E is their antioxidant activity Recently considerable evidence has accumulated which would indicate that their physiologic actions may be the result of this characteristic Oxygen consumption and carbon dioxide elimination is greatly increased in the dystrophic muscle and the consumption of oxygen by the dystrophic muscle is reduced dramatically by the administration of tocopherol to the animal or by the addition of tocopherol to the muscle in vitro before the uptake of oxygen is measured Vitamin A and carotene are particularly sensitive to oxidative destruction in the presence of unsaturated fats and vitamin E apparently offers them considerable protection both in the cell and in the alimentary tract [20]

Clinical Aspects—Experimental work with animals has stimulated observers to seek ways of applying their information to the problems of clinical medicine. How

19 Evans, H M and Burr G O Development of Paralysis in the Suckling Young of Mothers Deprived of Vitamin E, J Biol. Chem. 76: 273 (Jan) 19 8.

20 Hickman, K. C. D Harris, P L. and Woodside M R. Interrelationship of Vitamins A and E, Nature 150:91 (July 18) 194_

ever, there appears to be general agreement that vitamin E is of no value in the treatment of sterility The possibility that it may be of value in the treatment of habitual abortion requires further study Also, although vitamin E has been suggested in the treatment of such degenerative conditions as amyotrophic lateral sclerosis, further work seems to be required to establish the value or lack of value of this vitamin in such conditions It appears that patients with muscular dystrophy have neither a primary lack of vitamin E nor a deficiency secondary to poor absorption or chemical distribution of tocopherol [21] Extensive studies of progressive muscular dystrophy have shown that administration of neither alpha tocopherol nor wheat germ oil has any effect on the disease in man [22] However, it is still conceivable that in this disorder there may be some interference with intermediate steps in the utilization of alpha tocopherol Recently Milhorat and Bartels [23] have suggested that such a defect exists Current evidence does not indicate that vitamin E is useful in the treatment of any primary neurologic disorder

In instances in which patients were given small doses of vitamin E no toxic reactions have been reported Administration of large doses of wheat germ oil have given rise to only minor symptoms

VITAMIN K

Chemistry—Vitamin K has been shown to be essential to human nutrition [24] Natural vitamin K was first isolated from alfalfa and proved to be 2 methyl 3 phytyl-1 4 naphthoquinone It is a fat-soluble vitamin, easily destroyed by alkali strong acid, sunlight or artificial

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21 Minot A S and Frank H E Serum Tocopherol Its Relation to Failure of Vitamin E Therapy for Pseudohypertrophic Muscular Dystrophy Am J Dis Child **67**: 371 (May) 1944

22 Shank R E Gilder, H and Hoagland C L. Studies of Diseases of Muscle I Progressive Muscular Dystrophy Clinical Review of Forty Cases Arch Neurol & Psychiat **52**: 431 (Dec) 1944 Pappenheimer A M Muscular Disorders Associated with Deficiency of Vitamin E Physiol Rev **23** 37 (Jan) 1943

23 Milhorat A F and Bartels W E The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy Science **101** 93 (Jan. 26) 1945

24 Dam Henrik The Antihaemorrhagic Vitamin of the Chick Occurrence and Chemical Nature Nature **135** 652 (April 7) 1935 Butt H R Snell, A M and Osterberg A E The Use of Vitamin K and Bile in Treatment of the Hemorrhagic Diathesis in Cases of Jaundice Proc Staff Meet Mayo Clin **13** 74 (Feb 2) 1938 Warner E D Brinkhous K M and Smith H P Bleeding Tendency of Obstructive Jaundice Prothrombin Deficiency and Dietary Factors, Proc Soc. Exper Biol & Med **37**: 628 (Jan) 1938

light and has been prepared synthetically Another natural vitamin K vitamin K_2, was first isolated from putrefied fish meal Its exact structure is not known but is suspected to be 2 methyl 3 difarnesyl 1,4 naphthoquinone

Many synthetic substances which possess a quinoid nucleus have vitamin K activity Of all the naphthoquinone derivatives studied which displayed some degree of vitamin K activity 2 methyl-1 4-naphthoquinone has proved to be the most active Some investigators have found this compound to be three times as potent, on the basis of weight as vitamin K_1 Because of the usefulness of the compound in clinical medicine the Council on Pharmacy and Chemistry of the American Medical Association authorized menadione" as a nonproprietary name for this substance The compound is only slightly soluble in water [25] Its structural formula is shown in figure 2

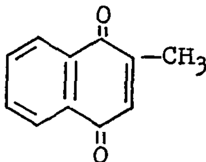


Fig 2—The structural formula of menadione.

The need for a water soluble material with vitamin K activity led to the testing of many other compounds Most of the water soluble compounds which have vitamin K activity are basically 2 methyl 1 4 naphthoquinones or the corresponding hydroquinone Such compounds as 4-amino 2 methyl 1 naphthol hydrochloride and sodium 2 methyl 1 4-naphthohydroquinone 3-sulfonate are water soluble and have been useful in clinical treatment They are not as active as menadione but are sufficiently active to produce the desired clinical results

25 Fieser L F The Chemistry of Vitamin K, Ann. Int. Med. 1•1 648 (Oct.) 1941

Sources—Vitamin K is distributed widely in nature and among its richest sources are green leaves Chlorophyll-bearing parts of the plant usually contain the largest amount of vitamin K Alfalfa and spinach are rich in the vitamin, and cabbage, cauliflower carrot tops, soy bean oil and seaweed are all good sources In general, seeds, fruits and roots contain considerably less vitamin K than do green leaves Most animal materials contain little vitamin K, milk and eggs contain small amounts However pork liver is an extremely rich source of this vitamin Vitamin K_2 occurs in many bacteria, whereas yeast, molds and fungi contain little or no vitamin K.

Requirements—The exact minimal requirements for vitamin K have not yet been determined The requirement for vitamin K is usually satisfied by any acceptable diet except perhaps for the infant in utero and during the first few days of life It has been suggested that newborn infants require little vitamin K and that possibly 1 microgram of synthetic vitamin K is a sufficient daily amount A dose of 1 to 2 mg of pure vitamin K_1 or a synthetic compound exhibiting vitamin K activity is known to be adequate for correcting deficiency of vitamin K It is known that the need for vitamin K is increased in cases of diarrhea and inadequate intestinal absorption As much as 40 mg of menadione may be required to correct the hypoprothrombinemia produced in man by the administration of dicumarol •

Absorption and Storage—It is necessary that adequate amounts of bile salts be present for proper absorption of natural vitamin K. Clinical experience has indicated that vitamin K is not absorbed through the colon or upper part of the ileum but is absorbed readily through the upper part of the jejunum In recent reports emphasis has been placed on the fact that if excessive amounts of liquid petrolatum are administered with meals proper absorption of this vitamin may be prevented

Apparently vitamin K is not stored easily in the body Clinical investigation indicates that the little that is stored in the body is stored in the liver Vitamin K has not been found in the urine or in human bile, but it has been found in the feces It remains to be established whether the vitamin K found in feces is there because

of the presence of micro organisms known to contain vitamin K or because of actual excretion of the substance. Some investigators have held the opinion that man obtains some of his supply of vitamin K from intestinal organisms, but this has not been definitely proved Prothrombin deficiency can be produced in animals by administration of sulfaguanidine succinyl sulfathiazole sulfapyrazine or sulfadiazine, prothrombin deficiency is prevented when vitamin K is administered This action has been explained on the basis of the effect of these drugs on Escherichia coli in the intestinal tract.

Physiologic Action—Little is known concerning the precise action of vitamin K in the animal organism It is known to pass readily from mother to fetus and to be associated intimately with normal physiologic function of the liver Avitaminosis K in man from any cause results in a decrease in the concentration of prothrombin of the blood, the prothrombin content of the blood increases rapidly after the administration of vitamin K Prothrombin administered orally does not show vitamin K activity This indicates that the vitamin does not form a part of the prothrombin molecule The manner in which vitamin K participates in the formation of prothrombin is not known It has been suggested that vitamin K is a reversible oxidation-reduction catalyst More recently a hypothesis has been reported which suggests that the antihemorrhagic effect of vitamin K and its synthetic analogues is due to their biochemical degeneration to phthalic acid The authors of this hypothesis regarded phthalic acid as the true carrier of biologic activity [26]

(A discussion of vitamin K deficiency appears in chapter 21)

TOXICITY

Serious untoward reactions have not been observed in cases in which patients have been given reasonable therapeutic doses of either natural concentrates of vitamin K synthetic vitamin K_1 or any of the synthetic compounds now available commercially which exhibit antihemorrhagic activity Apparently blood pressure res

26. Shemiakin M M Schukina, L. A., and Schvezov J B Studies in the Vitamin K Group. II The Mechanism of Biological Action of Vitamin K and of its Synthetic Analogs, J Am. Chem. Soc. 65:2164 (Nov) 1943

piration, permeability of capillaries or urinary excretion have not been affected after administration of any of these compounds However, oral administration of doses of menadione as large as 180 mg to human beings have caused vomiting and porphyrinuria These huge doses, however, are so obviously greater than those employed for therapeutic use that at present it appears safe to continue therapeutic administration of these synthetic compounds *As a rule, hyperprothrombinemia* is not produced in man when large doses of vitamin K are administered

Part II

NUTRITIONAL NEEDS

CHAPTER XII

RECOMMENDED DIETARY ALLOWANCES

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and
HENRY C. SHERMAN

When in 1940 the National Research Council reestablished its Committee on Food and Nutrition—now known as the Food and Nutrition Board—one of its first assigned functions was to formulate quantitative goals to serve as a basis of reference in planning diets and food supplies It was and is believed that these goals or guides would best be exactly what is implied in a literal interpretation of the carefully chosen words "*recommended dietary allowances*"

The term "recommended allowances" rather than standards was adopted to avoid implication of finality or rigidity and also to avoid confusion inasmuch as the word standards had already been used for somewhat different purposes by the League of Nations and by the United States Food and Drug Administration The standards proposed by the League of Nations had been an excellent stepping stone but had been formulated before the full development of the information available to the Food and Nutrition Board when it was actively engaged in formulating the recommendations which it was especially urged to present by the time of the National Nutrition Conference held in Washington in May 1941 The purpose of this conference and of the Board was to aid in pointing the way to nutritional betterment while the Food and Drug Administration had the more static task of setting so-called standards which for legalistic reasons must carefully avoid exceeding the actual (minimal) requirements of normal nutrition as it was previously understood

It is clearly the conviction of the Board (as it is our conviction) that the full efficiency of the movement for nutritional betterment may well involve materially

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higher intakes of some nutrients than those which barely suffice to maintain the minimum of nutritional well being accepted as normal in the past.

Hence, as the recommendations of the Food and Nutrition Board should not be called standards, they also should not be called requirements for the word requirement is usually taken to mean that amount which in a given case just suffices to cover the rock bottom minimum" of normal nutrition When several cases are averaged this average or mean is a figure about midway of the range of the individual cases If only this average amount were allowed to each person, the needs of about half the people would be met, while the other half would get less than enough to cover their needs The allowance should cover the needs not only of half but of practically all the persons whose food supplies are being (or are to be) planned This then, is the first and most obvious reason why the recommended allowances should be (and have been) set on a general level higher than that of the average of measured minimum requirements

There is also another reason not quite so obvious but promising to be perhaps equally important. This is the fact that with some nutrients—it is not yet known how many—step-like increases of intake above the requirement level confer correspondingly increased benefits in amounts up to levels well above that which meets requirement in the sense of preventing any sign of deficiency or shortage With nutrients such as calcium and vitamins A and C of which this has been shown to be true to an important degree it becomes especially logical that there should be liberality in formulating recommended allowances for such individual nutrients In fact it seems more than logical, it seems essential if these recommendations are to play the full part that they should in guiding persons to improved nutritional well being

Thus judgment does enter into the setting of the recommended allowances but this does not mean that these are as some critics have called them 'merely arbitrary" Rather they are based on objective measurements of minimum requirement, to the average of which in the case of each nutrient is added what is scientifically deemed to be a reasonable allowance to

cover individual variations plus a modest margin of some individual nutrients in recognition of the difference between minimal adequate and optimal intakes

We believe that the consensus of opinion of nutrition experts agrees with that of the Food and Nutrition Board that the general level of the recommended allowances is such that *no substantially lower level could be expected to yield equally good results with all persons and in long time experience*

Surplus intakes of most of the nutrient factors can be regarded either with indifference or as a kind of extra insurance, but obviously the case of food calories is different from other nutrient factors in that consumption of a considerable surplus leads to overweight.

BASES OF THE QUANTITATIVE RECOMMENDATIONS [1]

CALORIES

In the words of the Board, 'The proper calorie allowance is that which over an extended period will maintain the body weight (or rate of growth) at the level most conducive to well being' Height age, sex, muscular activity and environmental and genetic factors should all be taken into consideration and due account should be taken of the concept of 'ideal weight' as developed through the studies (still in progress) of life insurance experience and of the United States Public Health Service. Obviously single values cannot be equally accurate for different individuals whose needs are influenced by so many circumstances Hence it is suggested that the recommended calorie allowances be regarded as subject to modifications of plus or minus 15 to 20 per cent according to conditions

The energy allowances for adults are based on many studies, with normal healthy persons of (1) the food consumption (2) the oxygen consumption or carbon dioxide production or both under varying conditions of activity (3) the relation between intake and output of carbon and nitrogen in balance experiments or (4) the amounts of heat given off in a calorimeter by individuals engaging in different activities The results of such investigations support the adoption of 3 000

1 For fuller discussion and explanations, see Recommended Dietary Allowances, Revised 1948, Washington, D C., National Research Council Reprint and Circular Series no. 129 October 1948.

calories per day as the energy allowance for the 154 pound (70 Kg) man who is physically active but not doing heavy work and of 2,400 calories for the 123 pound (56 Kg) woman of similar activity Allowances are also recommended for sedentary and more active men and women and for the pregnant and lactating woman The allowance for the latter half of pregnancy is for the sedentary pregnant woman The allowance of 3 000 calories for the period of lactation is aimed at meeting the entire energy requirement of the infant in addition to that of the mother

Keys[2] reviewing the subject of the calorie requirement of adult man, comes to the conclusion that the recommended allowances in current use are too high and says that in the majority of cases insistence on the consumption of the recommended or 'required calories would clearly result in obesity" On the other hand *Science News Letter*[3] reports that the Food and Agriculture Organization of the United Nations proposes for an active man weighing 144 pounds (65 Kg) an allowance of 3 200 calories Computed to 154 pounds (70 Kg) the body weight for which the National Research Council recommends 3 000 calories, the allowance would be 3 422 calories which is an increase in round numbers of 400 calories over the National Research Council allowance If the suggestion of the National Research Council that the recommended calorie allowances be regarded as subject to modifications of plus or minus 15 to 20 per cent according to conditions" is followed, the maximum range for the physically active man would be 2 400 to 3 600 calories which would include the figure proposed by the Food and Agriculture Organization committee. Keys makes no statement in his review as to the reduction from 3 000 calories which he would propose for the physically active man but it would seem from his discussion that the resulting figure might well fall within this range of 2 400 to 3 600 calories and that, therefore on the whole 3 000 calories daily may still be considered a satisfactory average allowance for the physically active man weighing 154 pounds (70 Kg) It should always be kept in mind that the National

2 Keys, A The Calorie Requirement of Adult Man Nutrition Abstr & Rev 19:1 (July) 1949 Energy Requirements of Adults Chapter XIII th s Handbook

3 Well Fed Standards Set Science News Letter 56:210 (Oct. 1) 1949

Research Council recommended allowances are for the 154 pound (70 Kg) man and the 123 pound (56 Kg) woman In all studies of food consumption by individual persons therefore body weights should be determined and comparisons with the recommended allowances made only after computing the food intakes to 70 Kg for men and 56 Kg for women In addition only data on persons in good nutritional status should be used in judging the recommended allowances

Energy allowances for children have been arrived at largely through many studies of the food consumption of healthy children known to be growing normally These studies have been of two types, those in which averages for groups living in institutions have been obtained and those in which the food consumption of individual children whether living in institutions or in their own homes has been determined More of such studies carried on over longer periods and, in addition determinations of the actual energy expenditure of children in their various activities are needed Meanwhile the recommended allowances may be used satisfactorily if allowance is made for the fact that children of the same age differ sometimes greatly, in size and activity These differences should always be taken into account For example a child who is above average size for his age and normally active will require more food than a child of the same age of average size who is equally active Children who for any reason do not obtain calories enough will *show it in loss of weight or failure to grow* at a normal rate

It should be kept in mind when the recommended allowances for children are being used that they are only average figures for the middle age of the various age ranges A table based on average weight for age which gives the ranges in calories per kilogram and calories per pound of body weight per day for the various age groups will be found in Rose s Foundations of Nutrition [4]

PROTEIN

The amounts of food protein required for the maintenance of nitrogen equilibrium in healthy adults had already received the attention of investigators before the turn of the century and by 1920 it was possible

[4] MacLeod, G and Taylor C. M Rose s Foundations of Nutrition, ed. 4, New York, The Macmillan Company 1944 p. 81.

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2 Keys A The Calorie Requirement of Adult Man Nutrition Abstr & Rev **19** 1 (*July*) 1949 *Energy Requirements* of Adults Chapter XIII this Handbook

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[4] MacLeod G and Taylor C M Rose's Foundations of Nutrition ed. 4 New York, The Macmillan Company 1944 p. 81.

to compile the results of over 100 nitrogen balance experiments throwing quantitative light on this question These experiments had been made in the course of 25 independent investigations including work in several countries[5] Calculated to a basis of 70 Kg of body weight they averaged 44 4 Gm. (44 3 Gm. for men and 44 6 Gm for women) With the addition of 50 per cent to cover both individual differences in need and variations in the nutritive efficiency of the protein of different diets, there resulted a recommended allowance of 1 Gm of protein per kilogram of body weight per day which had been rather widely used as a standard for normal maintenance dietaries since 1920 and which was taken as an already accepted starting point in the "Recommended Dietary Allowances" published by the National Research Council in 1941 and reaffirmed in 1945 and again in 1948 Recent advances in scientific knowledge of the chemistry and physiology of the proteins have in some quarters tended toward an undiscriminating increase of dietary protein. Scientifically however, it is discrimination rather than mere openhandedness that is needed In certain medical and surgical conditions extra protein appears to be beneficial but in what conditions and to what degree are questions which belong to medical practice rather than to this paper which has to do with normal allowances for population groups

On this question of the maintenance need of normal human adults the protein allowance of approximately 1 Gm per kilogram of body weight per day has been amply confirmed as generously adequate by the consistent trend of investigations from the turn of the century to the time of writing In the first edition of the Handbook of Nutrition the independent study and interpretation of Professor H. B Lewis[6] assigns this allowance a safety margin of 50 to 100 per cent above actual normal requirement. Leitch and Duckworth[7] reached essentially the same result in their restudy of all available data and their use of a different mode of

5 Sherman H C Protein Requirement of Maintenance in Man and the Nutritive Efficiency of Bread Protein, J Biol. Chem. 41 97 1920 Chemistry of Food and Nutrition, ed. 7 New York, The Macmillan Company 1946 pp 209 210

6 Lewis, H. B. Proteins in Nutrition, J A. M. A. 120 198 (Sept. 19) 1942 Handbook of Nutrition, Chicago American Medical Association, 1943 chap 2.

7 Leitch I. and Duckworth, J The Determination of the Protein Requirements of Man, Nutrition Abstr & Rev 7:257 1937

statistical treatment which yields them an average maintenance requirement of about 50 Gm per day per normal person

Extensive new experimental evidence is now available from the experiments of Stare and his co workers,[8] who used 26 apparently healthy adults ranging in age from 19 to 50 years These included 5 medical students 5 home economics students, 3 graduate nurses 9 students from the Harvard School of Public Health and 4 research assistants On a basal low protein diet in which approximately 50 per cent of the protein was supplied by white bread 12 per cent by other cereals 30 per cent by vegetables and 8 per cent by fruit protein requirements were found to be between 30 and 40 Gm per 70 Kg of body weight When this diet was supplemented with meat or with wheat germ even less total food protein was required for the maintenance of healthy adults Stare and his co-workers concluded that the National Research Council s daily recommended allowance of 70 Gm of protein for an adult weighing 70 Kg is most generous and could if necessary be reduced to 50 Gm and still provide approximately 30 per cent margin above requirement Stare and co workers also consider the recent work of Bricker Mitchell and Kinsman [9] to be consistent with their own Thus the results of these extensive recent investigations directly on the protein requirement of normal adult maintenance indicate that the margin to cover differences of individual needs and of the protein of diets carried by the allowance of 1 Gm of protein per kilogram of body weight per day is at least as generous as was supposed when this level was first recommended in 1941 and reaffirmed in 1945 and again in 1948 The higher allowances recommended for women in the latter half of pregnancy and in lactation are based on the research of Macy and her associates [10] of Coons [11] and of others

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8 Hegsted D M Tsongas A. G Abbott D B and Stare F J Protein R qu rements of Adults J Lab Clin. Med 31 261 1946 Nut tion Rev 4:264 1946

9 Br cker M Mitchell H H, and Kin man G M The Prote n R quirem nts of Adult Human Subjects n Terms of the Protein Con ta ned n Ind dual Foods and Food Combinat ons, J Nutr t on 30:269 (Oct.) 1945

10 Macy I G Hunscher H A N ms B, and McCosh, S S Metabol sm of Women Du ing the Rep oductive Cycle I J B ol Chem. 86:17 1930 Shukers C. F Macy I G Donelson, E. N m B and Hunscher H A Food Intake n Pregnancy Lactati n and Reproductive R t in the Human Mother J Nutrit on 4 399 1931

11 Coons, C. M Stud e in M tabol sm During Pregnancy Oklahoma Agricultural and Me hanical Coll ge Agr cultural Exper mental Station Bulletin no. 223 1935 pp 9-113

*Recommended Daily Dietary Allowances**
Revised 1948
Food and Nutrition Board National Research Council

	Calories†	Protein (Gm)	Calcium (Gm)	Iron (Mg)	Vitamin A‡ (I U)	Thiamine§ (Mg)	Riboflavin§ (Mg)	Niacin (Nicotinic Acid)§ (Mg)	Ascorbic Acid (Mg)	Vitamin D (I U)
Man (154 lb 70 kg)										
Sedentary	2 400	70	1 0	12¶	5 000	1.2	1.8	12	75	‡
Physically active	3 000	70	1 0	12¶	5 000	1.5	1 8	15	5	‡
With heavy work	4 500	0	1.0	12¶	5 000	1.8	1 8	18	75	‡
Woman (123 lb 56 kg)										
Sedentary	2 000	60	1 0	12	5 000	1 0	1 5	10	70	‡
Moderately active	2 400	60	1 0	12	5 000	1 2	1.5	12	70	‡
Very active	3 000	60	1 0	12	5 000	1.5	1.5	15	70	‡
Pregnancy (latter half)	2 400‡	85	1.5	15	6 000	1.5	2.5	15	100	400
Lactation	3 000	100	2 0	15	8 000	1.5	3 0	15	150	400
Children up to 12 yrs										
Under 1 yr††	110/2 2 lb (1 kg)	3 5/2 2 lb (1 kg)	1.0	6	1 500	0 4	0 6	4	30	400
1-3 yrs (27 lb 12 kg)	1 200	40	1 0	7	2 000	0 6	0 9	6	35	400
4-6 yrs (42 lb 19 kg)	1 600	50	1 0	8	2 500	0 8	1.2	8	50	400
7-9 yrs (58 lb 26 kg)	2 000	60	1 0	10	3 500	1 0	1 5	10	60	400
10-12 yrs (78 lb 35 kg)	2 500	70	1.2	12	4 500	1.2	1 8	12	75	400
Children over 12 yrs										
Girls 13-15 yrs (108 lb 49 kg)	2 600	80	1 3	15	5 000	1 3	2 0	13	80	400
16-20 yrs (122 lb 56 kg)	2 400	75	1 0	15	5 000	1.2	1 8	12	80	400
Boys 13-15 yrs (108 lb 49 kg)	3 200	85	1 4	15	5 000	1 5	2 0	15	90	400
16-20 yrs (141 lb 64 kg)	3 800	100	1 4	15	6 000	1 7	2 5	17	100	400

* Objectives toward which to aim in planning practical dietaries The recommended allowances can be attained with a good variety of common foods which will also provide other minerals and vitamins for which requirements are less well known

† Calorie allowances must be adjusted up or down to meet specific needs The calorie values in the table are therefore not applicable to all persons but rather represent group averages The proper calorie allowance is that which over an extended period will maintain body weight or rate of growth at the level most conducive to well being

‡ The allowance depends on the relative amounts of vitamin A and carotene The allowances of the table are based on the premise that approximately two thirds of the vitamin A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A

§ For adults (except pregnant and lactating women) receiving diets supplying 2 000 alo [illegible] or [illegible] the allowance of [illegible] that figure are given fo [illegible]

does not imply that we can estimate the requirement of these factors within 500 calories but they are added merely for simplicity of calculation In the present revision riboflavin allowances are based on body weight rather than calorie levels Other members of the B complex also are required though no values can be given Foods supplying adequate thiamine riboflavin and niacin will tend to supply sufficient of the remaining B vitamins

¶ There is evidence that the male adult needs relatively little iron The need will usually be provided for if the diet is satisfactory in other respects

‖ The need for supplemental vitamin D by vigorous adults leading a normal life seems to be minimum For persons working at night and for nuns and others whose habits shield them from the sunlight as well as for elderly persons the ingestion of small amounts of vitamin D is desirable

‡ During the latter part of pregnancy the calorie allowance should increase to approximately 0 per cent above the preceding level The value of 2 400 calories represents the allowance for pregnant sedentary women

Allowances for children are based on the needs for the middle year in each group (such as 2 5 and 8 etc) and are for moderate activity and for *average weight* at the middle year of the age group

†† Need for infants increase from month to month with size and activity The amounts given are for approximately 6 to 8 months The dietary requirements for some of the nutrients such as protein and calcium are less if derived largely from human milk

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Further recommendations

Fat.—There is available little information concerning the human requirement for fat Fat allowances must be based at present more on food habits than on physiological requirements While a requirement for certain unsaturated fatty acids (the linoleic and arachidonic acids of natural fats) has been amply demonstrated with experimental animals the human needs for these fatty acids is not known In spite of the paucity of information on this subject there are several factors which make it desirable (1) that fat be included in the diet to the extent of at least 20 to 25 per cent of the total calories and ( ) that the fat intake include essential unsaturated fatty acids to the extent of at least 1 per cent of the total calories At higher levels of energy expenditure that is for a very active person consuming 4,500 calories and for children and adolescent persons it is desirable that 30 to 35 per cent of the total calories be derived from fat Since foodstuffs such as meat milk cheese and nuts etc contribute fat to the diet it is necessary to use separated or visible fats such as butter oleomargarine lard or shortenings to supply only one third to one half the amounts indicated

Water.—A suitable allowance of water for adults is 2 5 liters daily in most instances An ordinary standard for diverse persons is 1 milliliter for each calorie of food Most of this quantity is contained in prepared foods At work or in hot weather requirements may reach 5 to 13 liters daily Water should be allowed ad libitum since sensations of thirst usually serve as adequate guides to intake except for infants and sick persons

Salt.—The needs for salt and for water are closely interrelated A liberal allowance of sodium chloride for the adult is 5 grams daily except for some persons who sweat profusely The average normal intake of salt is 10 to 15 grams daily an amount which meets the salt requirements for a water intake up to 4 liters daily When sweating is excessive 1 additional gram of salt should be consumed for each liter of water in excess of 4 liters daily With heavy work or in hot climates 20 to 30 grams daily may be consumed with meals and in drinking water Even then most persons do not need more salt than usually occurs in prepared foods It has been shown that after acclimatization persons produce sweat which contains only about 0 5 gram to the liter in contrast with a content of 2 to 3 grams for sweat of the unacclimatized person Consequently after acclimatization need for increase of salt beyond that of ordinary food disappears

Iodine—The requirement for iodine is small probably about 0 00? to 0 004 mg daily for each kilogram of body weight, or a total of 0 15 to 0.30 mg daily for the adult This need is met by the regular use of iodized salt its use is especially important in adolescence and pregnancy

Phosphorus—Available evidence indicates that the phosphorus allowances should be at least equal to those for calcium in the diets of children and of women during the latter part of pregnancy and during lactation In the case of other adults the phosphorus *allowances should be approximately* 1 5 times those for calcium In general it is safe to assume that if the calcium and protein needs are met through common foods the phosphorus requirement also will be covered because the common foods richest in calcium and protein are also the best sources of phosphorus

Copper—The requirement for copper for adults is about 1 to 2 mg daily Infants and children require approximately 0 05 mg for each kilogram of body weight The requirement for copper is approximately one tenth that for iron A good diet normally will supply sufficient copper

Vitamin K—The requirement for vitamin K usually is satisfied by any good diet except for the infant in utero and during the first few days after birth Supplemental vitamin K is recommended during the last month of pregnancy When it has not been given in this manner it is recommended for the mother preceding delivery or for the baby immediately after birth

Folic Acid—Evidence for recognizing folic acid (pteroylglutamic acid vitamin B L casei factor or vitamin M) as an essential human nutrient is presented in the text *The quantitative requirement cannot be closely* estimated from evidence now available

The allowances for children were derived from compilations of data of nitrogen balances of children fed at different age levels These data indicate that protein intakes for each kilogram with which appropriate positive balances are obtained decrease from 4 to 3 5 Gm in infancy, 3 to 2 5 Gm in early childhood, 2 to 1 5 Gm in late childhood and adolescence, to the adult maintenance standard of 1 Gm The amounts in the accompanying table *represent approximately* these values The amounts actually required vary with the size of the child and with the quality of the protein

CALCIUM

The Food and Nutrition Board's original allowance *of calcium for normal adult maintenance* was based most immediately on the observations of Steggerda and Mitchell[12] and of Outhouse and her co workers[13] These investigators found that 11 of 16 subjects could *meet their maintenance needs with an allowance* of 10 mg of calcium per kilogram of body weight per day, the remaining 5 (or about 30 per cent) of the 16 persons studied required somewhat more With 10 mg of calcium per kilogram of body weight or 0 7 Gm per 70 Kg as a starting point, the maintenance allowance for men of this average size was set at 0 8 Gm in order to provide for individual variations of need It will be seen that the procedure here was similar to that followed in setting the maintenance allowance of protein but with a markedly lesser provision for variability in the case of calcium 0 8 Gm being scarcely 15 per cent above 0 7 Gm whereas the corresponding margin provided in the protein allowance is, as explained previously, at least 50 per cent

Many new data on calcium balance experiments under controlled conditions have been published since that time[14] *At the same time with the study of this* new evidence there has also been made a reexamination of all such evidence of strictly controlled experi-

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12 Steggerda F R. and Mitchell H H The Calcium Requirement of Adult Man and the Utilization of the Calcium *in Milk and in Calcium* Gluconate J Nutrition **17** 253 1939 Further Experiments on the Calcium Requirement of Adult Man and the Utilization of the Calcium in Milk ibid **21** 577 1941

13 Outhouse J Breiter, H Rutherford E Dwight J Mills R. and Armstrong W The Calcium Requirement of Man Balance Studies on Seven Adults J Nutrition **21** 565 1941

14 Cited by Sherman H C Calcium and *Phosphorus in Foods and Nutrition*, New York, Columbia University Press 1947

ments available to the beginning of 1948 from the viewpoint of the validity of each individual balance experiment in the light of present knowledge Seventy-three cases of wide geographic distribution thus appeared valid and obviously constituted a much broader basis than that used in 1941 In the light of all the evidence now available the Food and Nutrition Board has set its recommended allowance of calcium for normal adult maintenance at 1 0 Gm per day Statistically this covers the needs of all but about one in one hundred of the normal adult population The extended investigations of Leverton and Marsh [15] and of McKay and her associates [16] covering together about 150 studies made on what may be designated as a somewhat more observational plan than that of the 73 cases previously mentioned likewise led to the same recommendation of 1 Gm as did also the more recent work of Roberts Kerr and Ohlson [17] With so much evidence from direct human experience the strong confirmatory evidence from animal experimentation that liberal calcium intakes tend to produce exceptionally satisfactory life histories [14] need barely be mentioned The same maintenance allowance is recommended for women as for men despite their smaller average size in order to insure ample stores in preparation for maternity The higher allowances for pregnancy and lactation are intended to provide for the growth of the fetus with placenta etc and for milk production These increased needs are indicated by the observations of Macy and co workers Coons and others [18] The relatively liberal allowances of calcium recommended for children now have the added support of Macy s [19] long time balance experiments with 21 children of 5 to 12 years of age

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15 Leverton R. M, and Marsh A. G One Hundred Studies of the Calcium Phosphorus Iron and Nitrogen Metabolism and Requirement of Young Women Nebraska Agricultural Experiment Station Research Bulletin no 125 1942

16 McKay H Patton, M B Ohlson M A, Pittman M S Leverton, R M Marsh A G Stearns, G and Cox, G Calcium, Phosphorus, and Nitrogen Metabolism of Young College Women J Nutrition 24 36 1942 McKay H Patton M B Pittman M S Stearns G and Edelblute N The Effect of Vitamin D on Calcium Retentions, ibid. 26:153 1943

17 Roberts, P H Kerr C H and Ohlson M A. Nutritional Status of Older Women Nitrogen Calcium Phosphorus Retentions of Nine Women J Am. Dietet. A 24:29 1948

18 Macy Hunsche Nims and McCosh and Shukers. Macy Donelson, Nims and Hunscher [30] Coons.[31]

19 Macy I G Nutrition and Chemical Growth in Children. Springfield, Ill Charles C Thomas, Publisher 1942 vols. 1 and 2.

PHOSPHORUS

Phosphorus enters so widely into the structure and functions of both plants and animals including man, as to give rise to the saying " if the biographies of the elements could be written, that of phosphorus would be the most interesting of all" Yet this wide spread and relatively abundant distribution of phos phorus in plant and animal tissues and products makes it probable that dietaries of ample protein and calcium content can normally be trusted to supply sufficient phosphorus without special planning therefor Hence it does not seem necessary to include a column of figures for phosphorus in the table of recommended allowances nor to carry the discussion of phosphorus requirement further for the purposes of this paper Additional discussion of phosphorus requirements may be found under Further recommendations in the accom panying table

IRON

So far as the maintenance requirement of healthy men is concerned, what has just been said of phosphorus might also be said of iron but, because of uncertainties as to the relation of iron intake to some of the anemias it was deemed wise by the Food and Nutrition Board to continue for the present the allowances which have been customary in former years In the cases of preg nant and lactating women and of growing children liberal allowances of iron are more clearly correlated with nutritional well being and so there has been relatively little effort to fit the allowances closely to absolute minimal needs The allowances of iron rec ommended in the accompanying table are thus avowedly liberal for reasons which are believed to be good even if they still await further clarification

VITAMIN A

Perhaps greater divergence of judgment has existed as to the requirement for vitamin A than for any other equally well known dietary essential Three facts contribute to this situation (1) lack of any generally accepted method for determining the requirement (2) the fact that human nutrition requires more units of vitamin A value when taken in the form of the precursor carotene than when taken as vitamin A itself and (3) the capacity of the body for storage of vitamin A (and perhaps in lesser degree of carotene) which

while a fact of great value in the nutrient economy, is an added complication in the experimental work of quantitative determination of the vitamin A requirement

The allowance of 5 000 international units per day for adults was based largely on the studies of Booher and co workers,[20] Blanchard and Harper[21] and Guilbert Howell and Hart[22] and on the critical evaluation of the literature by With[23] These studies indicated that the requirement is 25 to 55 units for each kilogram of body weight, or 2 000 to 4 000 units daily, for the adult and twice these amounts or more if the source is carotene Because approximately two thirds of the vitamin A value of the average diet in this country is contributed by carotene it was decided that 5 000 units would represent a fair over all allowance. The allowances for pregnancy and lactation were somewhat arbitrarily increased over those for other adults by amounts estimated to meet the added needs

Because few studies indicating requirements have been made with children, the allowances were formulated on the basis of the judgment of the referees and *on calculations based on weight* *It is generally agreed* that the vitamin A requirement is related to body weight rather than to energy expenditure If the requirements for children are computed according to *weight on the basis of Booher's highest estimate of the* need of the adult the values for boys for example, would be 550 units at 1 year of age 1 000 at 4 1 430 at 8 2 200 at 12 and 3 300 at 16 If it is assumed that *the requirements are relatively higher on the basis of* weight as in the case of protein and minerals and if these values are multiplied by appropriate factors (for example those from protein as 3 2 5, 2 and 1 5) values approximating the recommended allowances are

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20 Booher L. E. Callison E C and Hewston, E. M An Experimental Determination of the Minimum Vitamin A Requirements of Normal Adults J Nutrition 17 317 1939 Booher L. E and Callison, E. C The Minimum Vitamin A Requirements of Normal Adults II The Utilisation of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure ibid 18: 459 1939

21 Blanchard, E L and Harper H A. Measurement of Vitamin A Status of Young Adults by the Dark Adaptation Technic, Arch. Int. Med. 66: 661 (S pt.) 1940

22 Guilbert, H R, Howell, C E and Hart, G H Minimum Vitamin A and Carotene Requirements of Mammalian Species J Nutrition 19: 91 1940 Experiment Station Record 82 660 1940

23 With T K Absorption Metabolism and Storage of Vitamin A and Carotene—with Some Remarks on the Vitamin A Requirement, Copenhagen, Einar Munksgaard, 1940 p 263

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of thiamine are never large and are quickly reduced by disease surgical operation and other stresses, it was deemed wise to allow a factor of safety of 100 per cent and recommend 0 5 mg per 1 000 calories of food This will be regarded as liberal or not, according to whether one adopts the lower or the higher estimate of the amount of thiamine actually used in the nutritional utilization of 1 000 calories of food If for any reason the calorie intake is drastically reduced the thiamine allowance should not be allowed to fall below 1 mg daily When on the other hand the energy requirement exceeds 3 000 calories the thiamine allowance for each 1 000 calories in excess of 3,000 is 0.2 mg rather than 0 5 mg

Studies of the thiamine requirements of infants [5] have shown that the minimum requirement in infancy in relation to calories is similar to that of the adult With no satisfactory reports concerning the thiamine requirements of children on which to base recommendations it was assumed that the allowance for infants and young children would apply throughout childhood

The few studies which have been made of the thiamine requirement during pregnancy and lactation [26] suggest that it is higher in proportion to the calories than in the other groups An allowance of 0 6 mg per 1 000 calories has been recommended

RIBOFLAVIN

At the time of the formulation of the original table of allowances in 1941 the results of only two experiments were available for determining the riboflavin requirement of human nutrition one by Sebrell and Butler [27] and the other by Strong Feeney Moore and Parsons [28] In both studies it was found that with an intake of 2 mg the excretion did not equal that

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25 Knott, E M Kl ge S C and Schlutz F W Is B east M lk Adequate in M eting the Thiam ne Requirement of Infants? J Pediat. 22 43 1943 Knott E. M Kle ger S C and Tor s-Bacram nte, F Facto s Affecting the Thiamine Content of Breast Milk J Nutrition 25:49 1943

26 Oldham H Sheft, B B and Porter T Thiam ne and Riboflav n Intakes and Excretions During Pr gnancy Federation Proc 6 416 1947 Kaucher M Mo er E Z Richa ds \ J Will ams H H W rtz, A L. and Macy I G Human Milk Studies XX The D t of Lactating Women and the Collect on nd P eparation of Food and Human Milk for An lysis Am. J D s. Child 70 142 (Sept.) 1945 Roderuck, C. W lliams H H, and Macy I G Metabol sm of Women Dur ng the Reproductive Cycle VIII The Utilization of Thiamine During Lactat on J Nutrit on 32 249 1946

27 Sebrell W H and Butler R. E. R boflavin Deficiency in Man, Public Health Rep 53 . 8., 1938

28 Strong F M Feeney R. E., Moore B and Pa sons H T The Riboflavin Content of Blood and Urine, J B ol. Chem. 137:363 1941

obtained Amounts in excess of those here recommended are easily obtained in diets containing desirable amounts of milk, eggs and green vegetables

All the experimental evidence thus far cited as a basis for the recommended allowances of vitamin A values in daily dietaries were obtained directly from *work with human subjects The actual measurements* relate almost exclusively to the one function of dark adaptation in vision and the total periods that subjects were under observation were but extremely small fractions of a normal life cycle Inasmuch as vitamin A is known to serve other important functions as well as vision and as the use to be made of the allowances will presumably have the well being of entire lifetimes in view it is logical to interpret and apply the recommendations tabulated here in the light of the evidence of animal experimentation, in which the effects of different levels of intake of vitamin A have been measured in comparison with strict quantitative controls throughout entire normal life cycles Such experiments have already established the principle that increased dietary allowances of vitamin A up to levels distinctly more liberal than those of the accompanying table[24] induce improved life histories

THIAMINE

Thiamine is regarded as primarily concerned with the bringing of carbohydrates into forms for oxidation in the body and therefore special attention has been given to the relation between the calories of food energy concerned in nutrition and the amount of thiamine needed

Relationships found by different investigators vary widely In some of the studies of human subjects the amount of thiamine needed for the support of the utilization of 1 000 food calories has been less than 0 2 mg, while in other instances it has been as high as 0 5 mg On the basis of the evidence reviewed, the minimum requirement for the adult appears to be 0.23 mg or more for each 1 000 calories Since the body stores

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24 Batchelder E L Nutritional Significance of Vitamin A throughout the Life Cycle Am J Physiol **109** 430 1934 Sherman, H C Campbell, H L Udiljak M and Yarmolinsky H Vitamin A in Relation to Aging and to Length of Life Proc National Acad. Sc **31** 107 1945 Sherman H C and Campbell H L. Stabilizing Influence of Liberal Intake of Vitamin A ibid **31**: 164 1945 Sherman H C and Trupp H Y Further Experiments with Vitamin A in Relation to Aging and to Length of Life ibid. **35** 90 1949

principle presumably equally true for the human species that successive increases of the riboflavin level of the diet result in correspondingly increased benefits to nutritional well being up to levels much higher than those required for minimal adequacy[30] Doubtless, surplus intake of riboflavin above the amounts needed to prevent any specific sign of deficiency contributes in some way to the well being of the body's internal environment Hence riboflavin allowances should logically provide more liberal margins above minimal need than in the case of some other nutritional factors

Recent animal experimentation has changed the view which previously increased riboflavin allowances in parallel with muscular activity and the calorie value of the diet Accordingly the table, as revised in 1948 allows 1 8 mg of riboflavin for the 70 Kg man and 1 5 mg for the 56 Kg woman regardless of muscular activity In our opinion the proportioning of the riboflavin allowances to the different age and sex categories in the table is logically consistent with the scientific evidence but the evidence also suggests that a somewhat higher plane of liberality of riboflavin allowances throughout may be expected to contribute to superior results in the long run of lifetimes and successive generations

NIACIN (NICOTINIC ACID)

When the table of recommended allowances was first compiled no evidence had been obtained from determinations on human beings as to the quantitative requirements for niacin The values adopted were derived by comparing the requirement of the dog for prevention of blacktongue with the niacin content of diets of persons in whom pellagra had been prevented The amounts thus obtained were found to be approximately ten times the corresponding allowances for thiamine Since both niacin and thiamine function in the oxidation reduction systems of the body through which the energy of food is released it was not surprising to find a constant relation between

30 Sherman H C. Research on Influence of Nutrition upon the Chemical Composition of the Normal Body Washington D C Carnegie Institution of Washington Yearbook 1941 vol 40 p 87 Chemistry of Food and Nutrition, ed 7, New York The Macmillan Company, 1946 pp 373 3 6 Ellis L. N Zmachinsky A and Sherman H C Experiments upon the Significance of Liberal Levels of Intake of Riboflavin, J Nutrition [illegible]:153 1943 Murray A. Z Zmachinsky W C and Sherman H C Riboflavin as a Factor in the Adequacy of the American Food Supply Scient. Monthly 63:151 1946

obtained from the control diet, but with an intake of 5 mg urinary excretion increased sharply From these results a requirement of 3 mg was deduced In appraising the data the committee concluded that some what less than this amount might be satisfactory Another consideration was the relationship which had been shown in experimental animals between the thia mine and the riboflavin requirements a ratio of 2 to 3 The addition of 50 per cent to the 1941 thiamine allow ance of 1 8 mg for the physically active man receiving 3 000 calories gave a riboflavin allowance of 2 7 mg, the value then recommended

Since that time there have been two general trends of experimental evidence bearing on the question of the level of intake of riboflavin which should be rec ommended Experiments with human subjects for periods of up to about one hundredth of the length of a normal life cycle have shown that for such periods, 0 6 mg of riboflavin per 1 000 calories of food (or two-thirds as much as the 1941 recommendation) can support adult maintenance and moderate muscular activity without the development of pathological signs Under such conditions the level of urinary output of riboflavin is considerably less than that indicative of bodily saturation but is thought by some students of the subject to be indicative of fairly satisfactory bodily stores To those who confine their attention to the work with human subjects alone—with experimental periods never more than about one per cent of a normal life cycle and usually much less—it has seemed that the downward trend from 0 9 mg to 0 6 mg of ribo flavin per 1 000 calories in the work of 1943 and 1944 [29] was a closer fitting of allowances to actual needs

Meanwhile however animal experimentation closely controlled and with periods extending to entire adult life cycles or successive generations has shown that the full effects of differences of riboflavin intake may become apparent only in much longer segments of the individual or family life cycle than have been studied in man Such experiments with rats have established the

29 Williams R D Mason H L Cusick P L and Wilder R M Observations on Induced Riboflavin Deficiency and the Riboflavin Requirement of Man J Nutrition **25**: 361 1943 Keys A Henschel A Taylor H L Mickelson O and Brozek, J *Absence of Rapid Deterioration in Man Doing Hard Physical Work on a Restricted Intake of Vitamins of the B Complex* ibid **27**: 485 1944 Oldham H Johnston F Kleiger, S and Hedderich Arismendi H A Study of the Riboflavin and Thiamine Requirements of Children of Preschool Age, ibid *37* 435 1944

there is still lack of a sound basis for using their excretion after a test dose as an index of the nutritional status of a person with respect to niacin

In the light of experiences with pellagra in man it seems unlikely that on a well mixed diet furnishing the recommended amounts of all the other nutrients there would be any deficiency of niacin It should not therefore be necessary to estimate the niacin content of the dietary except in special cases and then as has been shown the niacin values of foods need to be used with reservations as to their reliability and with the thought clearly in mind that the amount of niacin needed is influenced by the level of tryptophan in the diet and by the activity of the intestinal bacteria.

FOLIC ACID (PTEROYLGLUTAMATES)

Space does not permit the reproduction here of the excellent review on folic acid prepared by Dr C G King for the National Research Council s publication Recommended Dietary Allowances [35] to which readers of the present paper are referred Its conciseness is such as not to permit of further condensation without too great loss Other reviews on folic acid are also available [36]

ASCORBIC ACID

The recommended allowances for ascorbic acid are based on a larger body of evidence as to human requirement than exists as yet for any of the other vitamins Much of this evidence has come from studies of the effects of graded intakes of the vitamin on its concentration in the blood plasma and the excretion of it in the urine Carrying out such studies Todhunter [37]

35 King, C G In Recommended Dietary Allowances Revised 1948 Washington, D C National Resea ch Council Reprint and C rcular Series no. 179 October 1948

36 Jukes, T H and St kstad E L R. Pteroyl lutamic Ac d and Rel ted Compound *Phys ol Rev* **28** 51 1948 W lch, A. O Heinle R. W Prt ha d J A and Salis H Influence of Pteroyl lutam c Acid on the Synthes s and Action of the Ant P rn c ous Anem a Factor Federation Proc **7** 300 1948 Spi T Experiences W th Fol c Acid, Ch cago, The Yearbook Publ sher Inc 1947 Jacobson S D Berman L Axelrod A. R. and Vond r H de E. C. Fol c Acid Therapy J A. M A **137**:8 5 (July 3) 1948 Darby W J The Physiological Effects of Pteroylglutamates in Man, V tamins and Hormones **5**:119 1947

37 Todhunter E. N and Fatze S A Comparison f the Ut lization by Coll ge Women of Equivalent Amounts of Ascorb c Acid in Red Raspberries and in Crystalline Form J Nutrition **19** 1 1 1940 Todhunter E. N and Robb ns R C. Observ t ons on the Amount of Ascorbic Acid Requ ed to Ma nta n Tissu S turation n Normal Adults *Ibid.* **19**:263 1940 Todhunt E. N Robbins, R. C., and McIntosh, J A. The Rate of Increase of Blood Pla ma Ascorbic Ac d after Ingestion of Ascorbic Acid (V tam n C) *Ibid.* **22**:309 194_

them The observation was taken as evidence in support of the computed values for niacin, and the recommended allowances were set at ten times those for thiamine There is still no direct evidence from work with human beings as to the niacin requirement, and the 10 to 1 relationship to thiamine is still recommended

Niacin values of foods which have been reported are in some cases quite paradoxical—for example those for eggs and milk are conspicuously low and yet these two foods have for years been known to be excellent pellagra preventives A possible explanation is found in the recent discovery [31] that as the essential amino acid tryptophan is decreased in the diet more niacin is required for normal growth Conversely on a diet low in niacin addition of tryptophan brings about improvement in growth This relationship may explain why eggs and milk are so effective in preventing pellagra They are excellent sources of tryptophan and, also milk has been shown to favor the intestinal synthesis of niacin Coulson and Stewart,[32] Perlzweig and his co-workers [33] and Sarett and Goldsmith [34] have shown that tryptophan can be converted to niacin in the human body

Another recent discovery which adds to the complexity of the problem is that niacin may be synthesized by bacteria in the digestive tract and utilized by the body The amounts thus obtained vary widely depending largely on the kinds of food eaten and perhaps also on the individual as host" Still another difficulty in the way of determining the niacin requirement of human beings is the incomplete knowledge concerning the end products of niacin metabolism Several end products have now been identified, but

31 Krehl W A Sarma, P S and Elvehjem C A. The Effect of Protein on the Nicot nic Acid and Tryptophane Requ rement of the Growing Rat J Biol Chem **162** 403, 1946 Krehl, W A. Henderson L. M de la Huerga, J and Elvehjem C A. Relation of Amino Acid Imbalance to Niacin Tryptophane Defic ency in Growing Rats ibid. **166:** 531 1946 Krehl W A Sarma P S Teply L. J and Elvehjem, C A. Factors Affecting the D etary Niacin and Tryptophane Requirement of the Grow ng Rat J Nutrit on **31:** 85 1946

32 Coulson R. A. and Stewart, C A. Metabol m of Nicotinamide Nicotinic Acid and Diethylamide of Nicot nic Acid (Coram ne) by New born and Premature Infants Proc Soc Exper Biol. & Med. **61:** 364 1946

33 Perl we g W A. Rosen F Levitas N and Rol nson, J The Excret on of Nicotinic Acid Derivati es after Ingestion of Tryptophane by Man, J Biol. Chem. **167** 511 1947

34 Sarett, H P and Goldsmith G A The Effect of Tryptophane on the Excretion of Nicotinic Acid Derivatives in Humans, J Biol. Chem. **167:** 293 1947

and co workers,[46] working with children in the age range 7 years 9 months to 12 years 6 months found that to reach saturation, intakes of 105 to 125 mg per day were required although the blood level could be kept above 0 7 mg per hundred milliliters on intakes of 65 to 75 mg (1 7 to 2 4 mg per kilogram of body weight)

In the case of nursing infants it is of interest to note that 16 ounces of average human milk (when the mother s dietary is satisfactory in all respects) supplies over 35 mg of ascorbic acid daily, between two and three times the amount present in the same quantity of fresh cow s milk and the latter contains sufficient of the vitamin to prevent scurvy Infants receiving mother s milk have been found to have plasma concentrations and excretion levels of ascorbic acid such as are found in the state of saturation in children and adults

There is considerable clinical evidence of which we cite a few examples to support recommending allow ances of ascorbic acid far above the amounts which just prevent scurvy Hess[47] reported cases of retarded growth restlessness and irritability in children with no symptoms of scurvy who showed prompt improvement when orange juice or tomato juice or a mashed potato was added to the day s dietary Lanman and Ingalls[48] found a close relationship between the rate of healing of surgical wounds in human beings and the body store of vitamin C as did also Crandon and his associates[49] indicating the advisability of high intakes of the vitamin by surgical patients Goldsmith and Ellinger[50] reported that in their patients giving evidence of a mild deficiency of vitamin C urinary excretion of the vitamin did not increase appreciably until

46 Roberts V M and Roberts L J A Study of the Ascorb c Acid Requirem nts of Children of Early School Age J Nutrition **24**: 25, 1942 *Roberts V M Brookes, M H Roberts L J Koch I and Shelby P* The Ascorbic Ac d Requ rements of School Age Girls b d **26**: 539 1943

47 Hess A F Scurvy Past and Present, Ph ladelphia, J B Lippin cott Comp ny 1920

48 Lanman T H and Ingalls T H Vitamin C and Healing of Wounds Ann. Surg **10**: 616 1937

49 Cr ndon J H Lun; C C and D ll D B Experimental Human Scurvy New England J Med **223**: 353 1940 J A M A. **115**: 1637, 1940 Lund, C C. The Effect of Su g cal Operat ons on the Level of Cevitam c Acid in Blood Plasma, New England J Med. **221**: 123 1939 Lund C C and Crandon, J H Human Experimental Scurvy J A. M A **116**: 663 (F b ?.) 1941

50 Goldsmith G A and Ellinger G F Ascorbic Acid in Blood and Ur ne after Oral Adm n tr tion of a Test Dose of V tamin C, Arch. Int. Med **63** 531 (Ma ch) 1939

Ralli,[38] Batchelder,[39] Fincke,[40] Hauck[41] and MacLeod,[42] with their respective co workers, although noting considerable individual variations among their subjects have obtained results showing close agreement of averages and indicating that to maintain ascorbic acid saturation of the blood plasma (1 to 1 5 mg per hundred milliliters) a daily intake of 1 4 to 1 7 mg of the vitamin per kilogram of body weight is required For the 56 Kg woman this would amount to a daily allowance of 78 to 95 mg and for the 70 Kg man, 98 to 119 mg In an extensive study of the concentration of ascorbic acid in the blood serum and white blood cells of one hundred members of the Royal Canadian Air Force[43] it was found that those subjects who received 78 mg of the vitamin daily were about 90 per cent saturated Haines and co-workers[44] have reported that in their subjects (men and women) a daily intake of 70 mg was not sufficient to maintain a state of saturation The recommended allowances of 70 and 75 mg for women and men respectively are therefore below the amounts needed for saturation

In studies with children 3½ to 5½ years of age, Hathaway and Meyer[45] found that the minimum intake to insure saturation was 31 mg per day while Roberts

38 Ralli E. P and Sherry S Adult Scurvy and the Metabolism of Vitamin C, Medicine **20**: 251 1941

39 Lewcowich T, and Batchelder E. L. Ascorbic Acid Excretion at Known Levels of Intake as Related to Capillary Resistance Dietary Estimates and Human Requirements J Nutrition **23** 399 1942

40 Fincke M L. and Landquist V L The Daily Intake of Ascorbic Acid Required to Maintain Adequate and Optimal Levels of the Vitamin in Blood Plasma J Nutrition **23** 483 1942 Brown A. P Fincke, M L Richardson J E Todhunter E N and Woods, E Ascorbic Acid Nutrition of Some College Students ibid. **25** 411 1943

41 Belser, W B Hauck H M and Storvick C A A Study of the Ascorbic Acid Intake Required to Maintain Tissue Saturation in Normal Adults J Nutrition **17**: 513 1939 Storvick C. A., and Hauck H M Effect of Controlled Ascorbic Acid Ingestion upon Urinary Excretion and Plasma Concentration of Ascorbic Acid in Normal Adults ibid. **23** 111 1942

42 Dodds, M L and MacLeod F L. Blood Plasma Ascorbic Acid Values Resulting from Normally Encountered Intakes of this Vitamin and Indicated Human Requirements, J Nutrition **27**: 77 1944 A Survey of the Ascorbic Acid Status of College Students ibid **27** 315 1944 Blood Plasma Ascorbic Acid Levels on Controlled Intakes of Ascorbic Acid Science **106**: 67 1947

43 Lowry O H Bessey O A. Brock M J and Lopez J A The Interrelationship of Dietary Serum White Blood Cell, and Total Body Ascorbic Acid, J Biol. Chem. **166** 111 1946 Linghorne, W J McIntosh W G Tice J W Tisdall F F McCreary J F Drake T G H Greaves A V and Johnstone W M The Relation of Ascorbic Acid Intake to Gingivitis Canad M A. J **54** 106 1946

44 Haines J E Klosterman, A M Hauck H M Delaney M A. and Kline A. B Tissue Reserves of Ascorbic Acid in Normal Adults on Three Levels of Intake J Nutrition **33** 479 1947

45 Hathaway M L and Meyer F L. Studies on the Vitamin C Metabolism of Four Preschool Children J Nutrition **21** 503 1941 Meyer F L. and Hathaway M L Further Studies on the Vitamin C Metabolism of Preschool Children ibid. **28** 93 1944

well above the minimum to prevent scurvy but below the levels needed for complete saturation do not seem excessive The same can be said of the allowances for children in the light of the observations cited

It should be noted that it is not difficult to attain these levels of intake on a well mixed diet in which liberal use is made of fruits and fresh vegetables As to whether the body should be kept in a state of saturation with respect to ascorbic acid not all workers in this field are agreed as yet but with the evidence at hand there would seem to be no question as to the desirability of keeping the intake far above that which merely protects against scurvy and comfortably above the allowances recommended by the National Research Council and its Food and Nutrition Board

VITAMIN D

Much study seems to support the view that 400 international units of vitamin D per day is sufficient in all cases and this amount is therefore given in the table for all categories for which vitamin D is recommended

VITAMIN K

'The requirement for vitamin K usually is satisfied by any good diet except for one critical period Special attention is required during the latter part of pregnancy and for the newborn infant' This statement in the Recommended Dietary Allowances' is followed by a discussion too concise to permit adequate abstracting here Interested readers will wish to examine the section in full in the 1948 publication of the National Research Council

CONCLUSION

It cannot be too strongly emphasized that the recommended dietary allowances with the exception of vitamin D are easily supplied by a good diet of common foods and that many different combinations of these foods at different cost levels can be used The best way to assure meeting the recommendations is to include in the diet every day certain types of foods in sufficient amounts Many agencies government and others have published dietary patterns to serve as guides in doing this One of the most widely used is that of the Bureau of Human Nutrition and Home Economics[54]

[54] National Food Guide AIS-53 Bureau of Human Nutrition and Home Economics Agricultural Research Administration, United States Department of Agriculture 1946

the concentration in the blood plasma was raised to 1 4 mg per hundred millimeters Sevringhaus and his co workers,[51] in studies of adult prison inmates, found correlations between the level of intake of the vitamin its concentration in the blood plasma and gum conditions Macy and her associates [52] found that children who showed no symptoms of scurvy after long periods on low intakes of ascorbic acid promptly developed such symptoms if infections occurred and that on recovery from the infections the symptoms of scurvy disappeared Harris and associates,[53] in studies of the effect of the level of intake of ascorbic acid on urinary excretion of the vitamin observed that common infections such as a cold lowered the output These observations in human beings are in agreement with those of several investigators who have found that infections increased destruction of ascorbic acid in the experimental animal indicating the need for increased intake in such conditions and for an intake of liberal amounts regularly as a measure of protection against infection or its toxins

In many well controlled experiments with guinea pigs it has been found according to King (personal communication) that 0 5 mg of vitamin C per day prevents scurvy 0 8 mg per day supports normal growth 1 0 mg per day supports teeth which are fairly normal externally but on histologic examination show abnormal structure 3 0 to 5 0 mg per day supports teeth which are fully normal internally and also normal bones while it takes over 5 0 mg per day for optimal resistance to diphtheria toxin For optimal results then at least 10 times as much of the vitamin is required as for prevention of scurvy In man it has been found that 10 to 20 mg daily will prevent scurvy Ten times this would give 100 to 200 mg as the amount required for best results This range is considerably higher than that already cited for women and men that is 78 to 119 mg Compared with either range the recommended allowances of 70 mg for women and 75 for men which are amounts

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51 Kybos E D Gordon E S Kimble M S and Sevringhaus E L. The Minimum Ascorbic Acid Need of Adults J Nutrition 27 271 1944

52 Hamil, B M Reynolds L Poole M W and Macy I G Minimal Vitamin C Requirements of Artificially Fed Infants Am J Dis Child. 56: 561 (Sept.) 1938

53 Harris L J Passmore R. and Pagel W Influence of Infection on Vitamin C Content of Tissue Lancet 2 183 193

is also an outstanding source of riboflavin Another example is that of the citrus fruits and tomatoes as outstanding sources of ascorbic acid These foods are most commonly eaten fresh whereas the leafy green and yellow vegetables, which in the fresh state furnish almost as much ascorbic acid as the citrus fruits and tomatoes lose considerable amounts in the processes of preparation for eating This not only reduces their contribution of the vitamin to the diet but also makes it extremely variable In planning dietaries for some special conditions and for certain groups, such as adolescent girls and pregnant and lactating women, attention must be given to selecting regularly foods of high nutritive quality in order to furnish the recommended allowances and at the same time avoid an excess of calories

Studies of the national food supplies and of food consumption in the United States lead to the conclusion that in general most Americans are consuming food calories about in proportion to their energy requirements These persons have safe margins as to protein and fat but need to consume more fruits vegetables and milk to assure attainment of entirely adequate diets Good use of the recommended dietary allowances will help to bring this about

in which, on the basis of their nutritive content and use, foods are classified into seven groups (commonly referred to as "the Basic 7") For each group is given the number of average sized servings the total of which from the seven groups will furnish the recommended allowances for protein, minerals and vitamins If more calories are needed to meet individual requirements they may be obtained either by using larger amounts from the seven groups or by adding, from a separate list, foods which serve chiefly as sources of calories An interesting demonstration of the use of this guide in judging the adequacy of three menus of extremely different pattern used in different parts of the United States will be found in the final section of the National Research Council circular [1] Several guides to the selection of adequate *family diets at various cost* levels have been published by the Bureau of Human Nutrition and Home Economics [55] These guides show the quantities of food for a week that will meet the recommended allowances

It should be kept in mind when any of the plans giving quantities for food groups are being used that inadequate diets can result if poor choices of food are continuously made due to the great variability among *the individual foods in a group For example* the vitamin A value of dark green leaves such as kale spinach and turnip greens may be 10 to 12 times as great as that of green nonleafy vegetables in the same group such as asparagus beans green peppers and peas Care should be taken to eat a variety of the foods within a group to avoid a shortage of some nutrient

Another important point to be kept in mind is that some individual foods make such unique contributions to the diet that it is difficult to replace them if they are not used Milk for example is so outstanding as a source of calcium that without it or its products (other *than butter) it is almost impossible to supply* the required amount of calcium from common foods Milk

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55 Helping Families Plan Food Budgets United States Department of Agriculture, Miscellaneous Publication no *662* 1948 Food for the Family with School Children AIS-71 Bureau of Human Nutrition and *Home* Economics Agricultural Research Administration, United States Department of Agriculture 1948 Food for the Family with Young Children AIS 59 Bureau of Human Nutrition and Home Economics Agricultural Research Administration, United State Department of Agriculture 1946 Food for Two AIS 21 Bureau of Human Nutrition and Home Economics Agricultural Research Administration United States Department of Agriculture 1945

CHAPTER XIII

ENERGY REQUIREMENTS OF ADULTS

ANCEL KEYS

For the past decade or so the central importance of calories in the diet has been obscured by the phenomenal developments in other aspects of nutritional science This tendency is documented by the leading textbooks The space accorded to energy calorie estimation and requirements including the problems of obesity and emaciation is only 11 per cent of the text in such standard works as Sherman s[1] and McLester s[2] books and 9 per cent in the work by Hawley and Maurer-Mast[3] Such works expound general principles and some illustrations but do not critically examine the problems of actual practice Moreover while there is a spate of review articles and treatises on other aspects of nutrition monographs on calories and energy requirements appear infrequently and usually begin with a semiapologetic or defensive statement There is a danger that energy requirements may be regarded as of minor importance but energy requirements will always be of interest[4], Calories in medical practice are just as important as they ever were[5] It appears however that the pendulum of interest is now beginning to return toward the older problems of calories The hard lessons of the recent war included many demonstrations that, on a varied diet the problem of quality is apt to be secondary to quantity For the world as a whole the foremost food problem con-

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1 Sherman H C Chemistry of Food and Nutrition, ed. 7 New York, The Macmillan Company 1946

2 McLester J S Nutrition and Diet in Health and Disease, ed. 5 Philadelphia W B Saunders Company 1949

3 Hawley E. E. and Maurer Mast, E. E. The Fundamentals of Nutrition Springfield, Ill Charles C Thomas, Publisher 1940

4 Orr J B and Leitch, I The Determination of the Calorie Requirements of Man, Nutrition Abstr & Rev 7: 509 1938.

5 DuBois, E. F and Chambers, W H. Calories in Medical Practice, in Handbook of Nutrition, Chicago, American Medical Association, 1943 chap. 4 pp. 55-69

horse power (1 H P =33,000 foot pounds per minute), or, in electrical units, is equal to 69 77 watts The calorie, then, can be used as a measure of mechanical or electrical work as well as for heat

When food is burned in the body the resulting energy may appear entirely as heat or partly as external work from which, in turn heat may be derived *In any case, the energy result is substantially the same as though the food were actually burned outside the body Both inside and outside the body this combustion uses oxygen and produces carbon dioxide in proportion to the fuel used but the exact proportion depends on whether carbohydrate fat or protein is burned* For the latter the residual nitrogen resulting from combustion (urinary nitrogen) may be measured to estimate the amount of protein burned One gram of urinary nitrogen results from the combustion of about 6 25 Gm *of protein which is associated with the release of 26 5* calories, the use of 8 45 Gm of oxygen and the production of 9 35 Gm of carbon dioxide. If only protein were being metabolized it would be possible to calculate the calories involved by any one of three measurements (1) urinary nitrogen (2) oxygen consumption and (3) carbon dioxide production

But ordinary metabolism always involves fat and *carbohydrate as well as protein Fortunately for each* of the three sources of food energy the consumption of 1 liter of oxygen corresponds to much the same energy release roughly 5 calories This allows the use of the ordinary metabolism machine, in which only oxygen use is measured *for all but the most precise* estimations of energy expenditure Such measurements however do not indicate the proportions of the *three nutrients which are being used. For this it is* necessary in the system of indirect calorimetry, to measure the urinary nitrogen and the carbon dioxide production as well as the oxygen used After allowing *for the protein metabolized the proportion of fat to* carbohydrate is indicated by the respiratory quotient since pure carbohydrate has an R Q (volume of carbon dioxide divided by volume of oxygen) of 1 0 *while for pure fat the R Q is about 0 73* The details may be examined in various textbooks (e g see ref 11 below) the important point is that these indirect means can be used to get accurate *values for the current level* of energy use and the nutrients providing that energy

tinues to be a *shortage of calories* On the other hand, in a few favored areas like the United States, the opinion is developing that the most serious nutritional fault may be overeating[6] In a simpler world without the disturbing factors of processed and otherwise disguised foods of the social pressures associated with eating and the frequent substitution of food concepts in personal psychodynamics man might more uniformly strike an ideal balance between caloric intake and requirements always assuming that an abundance of food is at hand But man is by no means such a perfect *animal in an ideal state of nature* Moreover, though the appetite is remarkably accurate, it may fail to adjust to the altered situations in disease In any case it is clear that the individual often needs guidance about his caloric intake

These questions about caloric requirements take their simplest form at the point of caloric balance, that is where the energy intake precisely balances the outgo. Unfortunately, a large proportion of the actual problems which have to do with calories are more complex The most obvious complications have to do with growth and changes in body weight In the United States nearly a third of the population is made up of persons who are still growing and whose energy intake should exceed the output so as to allow for growth in many areas (e g the Far East) half the population may be in this category Even with adults the establishment of exact caloric balance may not be the immediate problem in nutritional therapy In medical practice *the question of calories usually arises in connection* with problems of losing or gaining weight

UNITS OF MEASUREMENT

In medicine the customary unit of energy is the large calorie or kilocalorie which in some literature is distinguished from the small calorie of the chemist by an initial capital for the former It is precisely defined as the amount of heat *which will* raise the temperature of a kilogram of water 1 degree from 15 to 16 C In an ideal engine 1 calorie would do 426 9 Kg-M (or 3,087 foot pounds) of work The dissipation of heat at the rate of 1 calorie per minute in a perfect engine is equivalent to doing work at a rate of 0 0936

6. A Study of Impairments Found Among 10 000 Unselected Examinees II Weight, editorial Proc. Life Ext. Exam 1: 89, 1939 Rynearson, E. H and Gastineau, C. F Obesity Springfield, Ill., Charles C Thomas, Publisher 1949

thereby increasing the energy cost of all its movements In the second place to consider the requirement as simply the caloric balance point supposes the existing body mass to be ideal the provision of the balance requirement then would perpetuate whatever fault of emaciation or obesity may be present "[7]

It would seem desirable or even essential, to differentiate between three kinds of requirements (1) the simple balance requirement of a person in his current state, (2) the ideal requirement and (3) the therapeutic requirement The first of these is straightforward the energy expenditure at any given time may be estimated with considerable precision The ideal requirement however is a theoretical concept, it would correspond to the energy expenditure of a person of ideal weight for height who is maintaining an optimal activity level for his occupation and environment Finally the therapeutic requirement is that intake which is calculated to rectify a fault of body weight or tissue mass when this correction is achieved it is replaced by either the ideal or the balance requirement

Most discussions about caloric requirements are devoted to the ideal requirement although this is not always so specified Tables of caloric requirements or recommendations are almost all of the ideal requirement' type but they uniformly ignore many of the factors which certainly influence the ideal requirement Among these may be mentioned age physical environment clothing and shelter recreational custom and habitual tempo of movement

VARIETIES OF CALORIC EXPENDITURE

All textbooks on nutrition and biochemistry summarize the varieties of caloric expenditure and indicate how the total expenditure may be estimated as the sum of the energy losses associated with basal metabolism specific dynamic action and physical activity This last item physical activity, is the most troublesome and, being both large and highly variable is the prime reason why the factorial method of estimating caloric requirements often leads to erroneous conclusions An excellent summary of the factorial method is given by Orr and Leitch[4], elsewhere, I have indicated some of the difficulties[8]

8 K ys[?] The R finement of Metabol c Calculations For N tritional Purpo s nd tle Problem of Availability edito ial review J Nutrition 29:81 1945

In terms of energy the body makes little or no distinction between fuels taken into the body and the substance of the body itself. If the energy expenditure exceeds the energy intake, the substance of the body itself is used to make up the deficit. If the intake is excessive on the other hand, the bodily substance increases accordingly. *In either case the change of bodily substance* primarily involves fat and glycogen, although homeostatic mechanisms tend to preserve the latter from total depletion on the one hand and unlimited storage on the other. *The bodily protein is relatively insensitive to* the caloric balance except when a negative balance is continued (starvation), then it, too, is burned in increasing proportion as the reserves of fat and glycogen dwindle. Fortunately, the body is disinclined to change its mass of substance and normally a disbalance between energy intake and outgo tends to be automatically corrected by the appetite.

Finally, it should be observed that the body customarily uses food completely. With ordinary foods 95 per cent or more of the potential energy is extracted, *the energy value of the excreta is only of the order of* 5 per cent that of the diet. This fact, together with the facts already noted, means that there are several alternative ways of estimating the energy balance and *needs of the body. These are discussed in subsequent* sections of this article.

MEANING OF CALORIC REQUIREMENT

The term *'caloric requirement' is widely* used without clear definition. Obviously the question must be answered: Requirement for what?[7] The simplest definition is to consider the caloric requirement as that *intake which will just balance the current energy expenditure.* This definition has several limitations in actual practice if requirement is to be construed as a prescription to achieve and maintain an ideal state of nutrition *in regard to calories.* *'In the first place, the energy* expenditure tends to reflect within limits the calorie intake. The underfed organism conserves its expenditure, partly by a decline in basal metabolism and, more *important perhaps by a reduction in voluntary* activity. And the overfed organism increases its mass

7 Keys A The Calorie Requirement of the Adult Nutrition Abstr & Rev 19 1 1949

anorexia nervosa the total basal metabolism may be 40 per cent below the normal level for age and height[12], the subnormality of the basal metabolism in undernourished persons is less pronounced when calculated per unit of surface area of the body

There is extensive literature on the relation of basal metabolism to race and to climate The racial factor may be dismissed here on the ground that if it does exist—and this is a matter of controversy—it is relatively trivial The effect of climate is discussed separately below

Specific Dynamic Action—The basal metabolic rate can be maintained as such for only a few hours at a time the resting metabolic rate is altered either by the changes associated with beginning starvation or those incident to the ingestion of food The latter, under the heading specific dynamic action are discussed in an extensive and often confusing literature The ingestion of a meal raises the resting metabolism to an extent which is variable depending on the character and size of the meal[13] While estimates of the percentage of the total metabolizable energy of meals which appears as specific dynamic action vary from around 6[14] to 17[13b] per cent there can be no great error in assuming a general average of 10 per cent for all ordinary mixed diets This energy is 'lost' as heat and presumably is a pure waste in warm climates in cold climates the heat of specific dynamic action may be a valuable adjunct in the maintenance of body temperature

Physical (Muscular) Activity—The energy cost of physical activity includes perhaps a third to as much as 80 per cent of the total caloric expenditure Even

12 (*a*) Keys A Caloric Undernutrition and Starvation with Notes on Protein Deficiency J A M A. **138**: 500 1948 (*b*) Beattie J., and Herbert P H The Estimation of Metabolic Rate in the Starvation State Brit J Nutrition **1**: 185 1948 (*c*) Basal Metabolism During Recovery from Severe Undernutrition Brit. J Nutrition **1**: 192 1948 (*d*) Keys A Brozek J Henschel A Mickelsen, O and Taylor H L. The Biology of Human Starvation Minneapolis University of Minnesota Press, to be published

13 ( ) Wachholder K. and Franz, H Die spezifisch-dynamische Stoffwechselsteigerung bei gemischter Kost, Pflugers Arch f d. ges. Physiol. **247** 632 1944 (*b*) Glickman N Mitchell, H H Lambert, E. H and Keeton R W The Total Specific Dynamic Action of High Protein and High-Carbohydrate Diets on Human Subjects J Nutrition **36**: 41 1948

14 Benedict, F G and Carpenter T M Food Ingestion and Energy Transformations With Special Reference to the Stimulating Effects of Nutrients, Carnegie Institute of Washington Publication no. 361 1918

Basal Metabolism —All indirect estimates of the total energy expenditure by the factorial method begin with the basal metabolism The obligatory least energy expenditure of the body in the resting state must certainly be the first portion of the total caloric demand to be covered But as Krogh[9] pointed out long ago, *the basal metabolism as customarily measured is not* really the basal, that is least resting, metabolism, the rate is considerably less than this in sleep and somewhat less in ideal repose in the waking state The excellent basal metabolism standards of the Mayo Clinic[10] overestimate the true basal metabolism by something like 10 per cent[7] However, the customary measurement of basal metabolism is undoubtedly a good index of the true basal rate and the numerical error is sufficiently systematic to permit its use with correction, in calculations for total metabolism

A most important virtue of the basal metabolism is the fact that in normal persons it is subject to so little individual variation This means that in many cases the actual measurement may be dispensed with and the basal metabolic rate can be estimated within an error of perhaps plus or minus 10 per cent, from tables like those compiled by the Mayo Clinic For individual patients however the individual measurement should be made if there is the least question about the complete normality of the basal metabolism In normal persons including the majority of persons who are habitually underweight or overweight the mean true basal metabolic rate for men ranges from about 40 calories per square meter of body surface per hour at age 20 to about 35 calories at age 60 the corresponding values for women are about 35 and 31 calories[11] This means that for adults of average size the basal metabolism accounts for something like 1 600 calories per day in young men to perhaps 1 100 calories in older women Gross departures from these values are found in the presence of thyroid disturbances and in semistarvation In famine victims and patients with

9 Krogh A The Respiratory Exchange of Animals and Man New York Longmans Green & Co 1916

10 Boothby W M Berkson J, and Dunn H L Studies of the Energy of Metabolism of Normal Individual A Standard For Basal Metabolism With a Nomogram For Clinical Application Am. J Physiol. **116** 468 1936

11 DuBois E F Basal Metabolism in Health and Disease, ed. 3 Philadelphia Lea & Febiger 1936 pp 145 188

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12. (a) Keys, A. Caloric Undernutrition and Starvation with Notes on Protein Deficiency J. A. M. A. 138 500 1948. (b) Beattie, J., and Herbert, P. H. The Estimation of Metabolic Rate in the Starvation State, Brit. J. Nutrition 1 185 1948. (c) Basal Metabolism During Recovery from Severe Undernutrition, Brit. J. Nutrition 1 19-, 1948. (d) Keys, A. Brozek, J. Henschel, A. Mickelsen, O., and Taylor, H. L. The Biology of Human Starvation, Minneapolis, University of Minnesota Press, to be published.

13. (a) Wachholder, K., and Franz, H. Die spezifisch-dynamische Stoffwechselsteigerung bei gemischter Kost, Pflügers Arch. f. d. ges. Physiol. 247 6--, 1944. (b) Glickman, N. Mitchell, H. H. Lambert, E. H., and Keeton, R. W. The Total Specific Dynamic Action of High Protein and High-Carbohydrate Diets on Human Subjects, J. Nutrition 36 41 1948.

14. Benedict, F. G., and Carpenter, T. M. Food Ingestion and Energy Transformations With Special Reference to the Stimulating Effects of Nutrients, Carnegie Institute of Washington, Publication no. 261 1918.

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11 DuBois, E F Basal Metabolism in Health and Disease ed. 3 Philadelphia Lea & Febiger 1936 pp 145 188

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12 (a) Keys A Caloric Undernutrition and Starvation with Notes on Protein Deficiency J A M A **138** 500 1948 (b) Beattie J and Herbert P H The Estimation of Metabolic Rate in the Starvation State Brit J Nutrition **1** 185 1948 (c) Basal Metabolism During Recovery from Severe Undernutrition Brit J Nutrition **1** 192 1946 (d) Keys A Brozek J Henschel A Mickelsen, O and Taylor H L The Biology of Human Starvation Minneapolis University of Minnesota Press to be published

13 (a) Wachholder K and Franz, H Die spezifisch dynamische Stoffwechselsteigerung bei gemischter Kost, Pflugers Arch f d ges Physiol **247** 63 1944 (b) Glickman N Mitchell H H Lambert, E H and Keeton R W The Total Specific Dynamic Action of High Protein and High-Carbohydrate Diets on Human Subjects J Nutrition **36** 41 1948

14 Benedict, F G and Carpenter T M Food Ingestion and Energy Transformations With Special Reference to the Stimulating Effects of Nutrients, Carnegie Institute of Washington Publication no 361 1918

the bed-fast patient indulges in many movements in addition to those of the respiratory muscles More over, the absence of gross movement is no guarantee of muscular relaxation static work, in which movement is opposed by an external object or by antagonistic muscles, may involve relatively high rates of energy expenditure In the heaviest forms of manual labor and sports, where the total *daily* expenditure may range upward from 5 000 calories, the cost of physical activity completely dominates the metabolic picture

There are available numerous tables which purport to indicate the metabolic cost of different occupations and forms of activity These have some interest in that they indicate, for example, the broad differences between clerks and carpenters and the relative costs of sitting and standing But the fact is that the variations in the ways in which different persons work at the same job and the changing nature of work in modern technology make metabolic classifications by occupation extremely crude[7] Moreover, in the United States an increasingly large proportion of workers are not classifiable in the older more uniform crafts and trades Finally, the reduction in the hours of the work week and the substitution of mechanical for muscular force in almost all types of work means that often enough the metabolic cost of physical activity outside working hours in sports hobbies and avocations is more important than that on the job Such categories as 'desk worker, farmer and housewife have little or no significance for predicting energy needs without much more detailed specification

Body Size—The body size is of major importance with regard to both basal metabolism and the cost of muscular activity Although the basal metabolic rate is customarily considered as related to the body surface a direct relation to the body mass (weight) is evident If the body weight is raised to the power 0 7, it becomes closely proportional to the basal metabolism[15] The energy cost of moving the body (or its parts) is directly proportional to the weight of the body (or the parts concerned) so that in many types of physical activity such as walking the energy expenditure is simply proportional to the body

15 Kleiber M Body Size and Metabolic Rate Physiol Rev 27 511 1947 Galvao P E Human Heat Production in Relation to Body Weight and Body Surface, J Applied Physiol. 1:385 and 395 1948

weight[16] In some tasks, however, the energy cost of the physical activity has little relation to the body weight, these are primarily tasks in which it is necessary to exert large forces with little bodily movement The exact relation between body size and total metabolism must depend on the activity habitus, but in general it is probable that the simplest approximation would be $Cal = AW^n$, where A is a numerical constant, W is the body weight and n is something between 0 7 and 1 0

Climate —The effective external temperature, that is with due allowance for humidity and air movement as well as dry bulb air temperature influences the energy expenditure in several ways The general tendencies are clear and have been amply demonstrated by observation and experiment[17] Under hot conditions the activity tends to be curtailed to keep the body temperature within normal limits while cold has the reverse effect Shivering in the cold may raise the resting metabolism by 50 or even 100 per cent In addition to the effect on the activity, differences in the effective temperature when long maintained tend to alter the basal metabolism so that lower basal rates occur in the tropics[18] Recent studies on United States and Canadian troops on active duty in different climates suggest that for these men balance was attained according to the equation Cal per day=4660—15 9 T where T is the mean external temperature (Fahrenheit)[19] It should be observed that this relation pertains to very active young men who were, essentially 'camping out less climatic effect would be expected when the activity component is a smaller fraction of the total metabolism and when less time is spent out of doors For ordinary population groups in the United States it could be suggested that an allowance of perhaps 3 per cent of the total metabolism should be provided for each 10 degrees difference in the mean

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16 Erickson L E Simonson E Taylor H L Alexander H and Keys A The Energy Cost of Horizontal and Grade Walking on the Motor Driven Treadmill Am J Physiol. **145** 391 1945

17 Keys[7] Keys, Brozek Henschel Mickelsen and Taylor[34] chap 17

18 Eaton A G Basal Metabolic Rate of Normal Individuals in New Orleans J Lab Clin Med **24**:1255 1939 Macgregor, R. G S and Loh G L The Influence of a Tropical Environment Upon the Basal Metabolism Pulse Rate and Blood Pressure in Europeans J Physiol. **99** 469 1941 Ames A and Goldthwaite D A Influence of Cold Climate on Basal Metabolism United States Department of Army Office Quarter Master General Environmental Protection Series Report no 136

19 Keys Johnson R E. and Kark, R. M Environment and Food Intake in Man Science **105**:378 1947

external temperature. This would mean that if the caloric requirement at 70 F is 3 000 calories at 40 F and 90 F it would be, respectively something like 3,270 and 2 820 calories The true average effect may be greater or less than suggested here, but it seems certain that climate may not be overlooked in setting up caloric standards For persons living largely indoors the effect may be small but for persons working and living much in the open the effect is of real importance.

TABLES OF REQUIREMENTS AND RECOMMENDATIONS

Almost since the first recognition of the fact that people do have energy requirements which are most appropriately expressed in calories there has been a constant stream of tables and charts to afford guidance in practical dietetics The best known of these is currently the Recommended Dietary Allowances of the National Research Council[20] which in the United States at least, has superseded the older standards of the League of Nations[21] In general these tables have been devised to aid in organization of the feeding of population groups and in evaluating their food supplies With almost no exception the orienting philosophy behind them has been to emphasize the frequency and danger of undernutrition and to promote an abundance of food supplies In practice such tables have been widely adopted as a short-cut means of estimating nutritional status so applied that intakes less than the suggested standards are labeled deficient that is bad and all other intakes, even though excessive are accepted as sufficient and good."

Whatever may be the virtues of these tables for large population groups they are necessarily of little value for individuals or for small groups which may not be representative of the entire population. Even for large population groups such tables are not properly used as dietary prescriptions to achieve the *best* nutritional state in view of their bias in favor of insuring enough without regard to the possibility of too much These tables have been compiled largely by theoretical calculations from laboratory experiments with relatively few data from long time studies on

20. Recommended Dietary Allowances, Revised 1948, National Research Council Reprint and Circular Series no. 129 Washington, D C., 1948.
21 League of Nations Technical Commission The Problem of Nutrition, vol. 2 Report on the Physiological Bases of Nutrition, Official Report A12 (a) II B, 1936

caloric intake and actual nutritional status of people as they normally live As we shall see, nutritional surveys indicate that the tabular standards are often too high, and the detailed data from such surveys disclose individual variations of large magnitude Besides a systematic tendency to overestimate actual caloric requirements these tables oversimplify the questions by ignoring differences in climate in local activity customs and in age of adults

Caloric Intake in Surveys—Theoretically at least the mean caloric intake of a population group clinically judged to be 'well nourished' should be a useful estimate of the caloric requirement for the group This method was in fact crudely applied to form the basis for some of the first estimates of normal human requirements In more recent years however, food intake surveys have been largely used to 'prove the existence of various dietary deficiencies by showing that food intakes often fail to equal or surpass one or another arbitrary standard It is instructive however to point out that many recent surveys have been coupled with physical examinations of the persons concerned with the result that they provide data on the caloric intakes of persons who are clinically well nourished and are leading lives normal to their area and sphere of life Almost without exception these data indicate that such standards as the National Research Council 'Recommended Dietary Allowances [20] would provide overgenerously in the case of calories Discrepancies are particularly large in the case of women and for all older persons The survey findings some of which are indicated below lead inevitably to one of the following conclusions (1) The survey data are all systematically in error and substantially underestimate actual caloric intake or (2) a great many persons are habitually calorically starved even in the absence of any limitation in money or available food supplies, but this semistarvation is not clinically discernible or (3) the caloric requirements and recommendations used as standards are too high

Significant data are beginning to be available for normal men and women whose activities may be described as sedentary" physically active (men) or moderatively active (women) These are the lowest and the middle of the three activity (metabolic) levels distinguished by the National Research Council

and many other authorities It is generally agreed that in a large population group, the middle metabolic level, "moderately active," corresponds roughly with the mean metabolic level of the entire adult population

The National Research Council recommendations are 2 000 and 2,400 calories, respectively, for 'sedentary" and moderately active" women In comparison, survey findings on the actual caloric intakes of non emaciated normal women may be noted 1,930 calories in Toronto families,[22] 1,452 calories for American women of low and moderate income in the United States [23] 2 039 calories for moderately active college women in the United States,[24] 1 577 calories for white women and 1,443 calories for Negro women in North Carolina [5] 1 797 calories for active Michigan women over 40 years of age [6] 1 690 calories for obese college girls in Michigan [26] 2 187 and 2,137 calories for different groups of middle class English women [27] and 1 424 calories for active old women in England [28]

Survey data on men indicate a like discrepancy between apparent caloric intake and recommended values [29] Various technics—weighing questioning and homely measures (by cups and the like)—have been used in the several surveys cited, but they all tend to yield similar values and in fact, are in agreement with each other when simultaneously applied [30] It might be suggested however that all these methods under estimate calories in the intake Recent painstaking studies on the contrary, showed that all these methods

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22 *Patterson J M and McHenry E W A Dietary Investigation in* Toronto Families Having Annual Income Between $1 500 and $2 400 Canad Pub Health J **32**: 251 1941

23 Winters J C and Leslie R E A Study of the Diet and Nutritional Status of Women in a Low Income Population Group J Nutrition **26**: 443 1943 A Study of the Diet of Twenty Women in a Moderate Income Group J Nutrition **27**: 185 1944

24 Pittman M S, McKay H Kunerth B L. Patton M B, Edelblute N and Cox G *Caloric Intakes of Twenty Seven College Women* J Am Dietet. A **18**: 449, 1942

25 Milam D F A Nutrition *Survey of a Small North Carolina* Community Am J Pub Health **32**: 406 1942

26 Ohlson M cited by Keys

27 Widdowson E M and McCance R A Study of English Diets by Individual Method Women, J Hyg **36**: 293 1936 Widdowson E M and Alington B K Middle Class Diets in Peace and War Lancet **241**: 361 365 1941

28 Pyke M Harrison R Holmes S and Chamberlain K Nutritional Value of Diets Eaten by Old People in London Lancet **253**: 461 1947

29 Patterson and McHenry [22] *Pike Harrison Holmes and Chamberlain* [28] Wiehl, D G Nutritional Status of Aircraft Workers in Southern California I Diets of a Group of Aircraft Workers in Southern California Milbank Mem. Fund Quart **20**: 3 9, 1942

30 Widdowson, E. M and McCance R. A Food Tables: Their Scope and Limitations Lancet **244**: 230-232 1943

may yield data in good agreement but give a considerable overestimate for calories[31]

In other words, there is certainly no evidence or valid argument that the caloric intake data from surveys are generally or even frequently underestimates Since clinical undernutrition with regard to calories was not characteristic of the persons studied in these surveys it must be concluded that the recorded caloric intakes were *at least on the average equal to the* caloric expenditures It follows that, if such intakes fail to equal certain standards or recommendations then the fault is with the standards and recommendations, which must be indeed overestimates of the requirements

The sole remaining alternative to this last conclusion would involve the idea that a person who is clinically well nourished may when given an increased caloric intake expend that extra food energy on useful work without any change in his net body mass While underweight persons will often do more work when given more food[1 d] we know of no instance in which the body weight *does not also respond simultaneously In the well* nourished person there is no evidence that an increased caloric intake is accompanied by an equally increased level of physical activity The converse sequence is, of course well established an increased level of physical activity leads to a corresponding increase in food intake if food supplies are available

CALORIC NUTRITIONAL STATUS

It is certain that the continued consumption of less *food than corresponds to the caloric expenditure must* lead to relative emaciation and an excessive intake must lead to obesity For short periods these tendencies may be obscured by abnormalities in the hydration of the body but in the absence of other disease neither dehydration nor edema can long disguise the progressive effects of continued caloric imbalance[32]

Obviously then a changing body weight may permit an accurate inference about the caloric balance and roughly the alteration of intake needed to correct *this But what if as is more often the case the body* weight is not changing? Caloric balance may be achieved at widely differing levels of body weight and

31 Bransby E. R. Daubney C. G and King J Comparison of Results Obtained by Different Methods of Individual Dietary Survey Brit. J Nutrition 2: 89 1948

32 Newburgh, L. H Obesity Arch. Int. Med. 70 1033 1942

these involve correspondingly different levels of energy intake and expenditure A fat man needs much food to maintain caloric balance because he is heavy, every movement is energetically more expensive because of the greater mass of the body and its parts which must be moved The guide for the person whose weight is stable must be in the actual mass and composition of his body Any substantial departure from the ideal in these respects indicates the departure of the average previous food intake from the ideal

As a first approximation we may take the gross body weight and compare it with some standard The body weight standards given in all textbooks are in fact, merely the arithmetical averages of the body weight of apparently "normal' persons of specified age, sex and height [33] As such they indicate popular trends but do not necessarily indicate "ideal" weights For the latter it is suggested, with support from insurance mortality experience, that the ideal weight is lower than the actual normal average for all persons over 30 years of age [34] Another question is how to allow for differences in skeletal ("frame') size It is agreed that this is of importance and that a person of 'small' frame should weigh perhaps 5 per cent less than a person of 'medium frame of the same height, age and sex, an extra 5 per cent is suggested for the person of 'large frame [34] As yet there are no agreed criteria for frame classification

In the absence of quantitative tools the clinical judgment of the state of caloric nutrition is made on the basis of appearance and manual appraisal of the muscular development and the subcutaneous fat deposits There is no reason to suggest that this method is not actually both useful and fairly reliable [35] In effect, it attempts to estimate the body composition with emphasis on the relation of fat to other tissues

With any reasonable definition the inadequacy, sufficiency or excess of the previous diet should be reflected in the relative fat content of the body The principal difficulty with the usual clinical method besides the lack of numerical expression is that the subcutaneous fat may not always be an accurate index of the total

33 Medico-Actuarial Mortality Investigations Proc Actuarial Soc. Am. 1 1 1912

34 Ideal Weights For Women Stats Bull. Metrop Life Insur Co. 23 6 1942 Ideal Weights For Men ibid 24: 6 1943

35 Sinclair H M The Assessment of Human Nutriture, Vitamins and Hormones 6: 101 1948

fat of the body With the development of caliper methods for measuring the thickness of the skin[36] quantitative expression becomes possible and measures of this kind have already had some use in appraising the nutritional status of children[37] Roentgenographic methods for the same purpose are also being devel oped[38] The potentialities for the estimation of total bodily fat from the gross body density seem particularly promising at least for research[39]

As yet critical analyses and proper standards for the use of these indirect methods are inadequate for general application in nutritional work an intensive program at the Laboratory of Physiological Hygiene is aimed to improve this situation Though major reliance in the meantime must be placed on simple height-weight data the value and even necessity of a clinical appraisal must not be neglected An extremely inactive person that is one with a greatly subnormal muscle mass may actually be obese (fat) even though he has a body weight which is normal or even some what subnormal for his height On the other hand the devotee of athletics, in spite of a normal body weight may be undesirably lean, he may need more food to achieve a reasonable fat mass in his body Clinical examination should readily disclose the peculiarity in these cases

THE PHYSICIAN S TASK

The physician s task in regard to the caloric requirements of his patients is manifold and in many cases complicated It is not unfair to suggest that more

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36 Te hedebrugge A Ueber Messung des Fettpolsters Virchow s Arch. path Anat. Physiol **298** 640 1936-1937 Lauter S and Terhede b ugge A Ueber Fettansatz und F ttverte lung be m normalwichtigen Menschen Deutsche Arch klin Med **181** 181 1937 1938 Ueber Fettansatz und Fettschwund be Magerkeit (Magersucht) und Amagerung Deutsche Arch. kl n Med **181** 193 1937 1938 Ueber Fettansatz und Fettvert lung bei Fettsuchtigen Deutsch Arch kl n Med. **183** 91 1938 1939 Curet n T K Phys cal F tness Appraisal and Guidance St. Lou s C V Mo by Company 1947

37 Ruotsalainen A Die Fettpolsterd cke als Mass des E nahrung zustandes von Schulkindern *Ztschr f K nderh* **60** 648 1939 Boyn t n B The Phys cal Growth of Girls A Study of the Physical Growth From Anthropomet c Measurem nts on Gi ls Between B th and E ghteen Yea s Unive ty of Iowa Stud es Ch ld Welfa e **12** 1 105 1936

38 Stua t H C H ll P and Shaw C The Growth of Bone Muscle and Overlying Tissue as Revealed by Studies of Roentgenog ams of the Leg Area Monograph Society for Research in Ch ld Development, 1940 vol 5 p 1 Stuart H C and Sobel E H The Thickness of the Skin and Subcutaneous Tis ue by Age and Sex n Childhood J Ped at **28**: 637 1946 Reynolds E L and Asakawa, T The Measurement of Obes ty in Childhood Am J Phys Anthropol (n s) **6** 475 1948

39 Behnke A R. Feen B G and Welham W C The Specific G av ty of Healthy Men Body We ght — Volume as an Index of Obesity J A. M A **118** 495 1942 Rathbun E N and Pace N Studies on Body Composit on I The Dete mination of Total Body Fat by Means of the Body Spe ific Gravity J Biol. Chem **158**: 667 1945

often than not, it is shirked or incompletely done There are good reasons for this—lack of instruction in the medical schools, poverty of textbook discussion and deficiencies in data from research—but these do not remove the responsibility which automatically falls on every consultant Besides the gross cases of emaciation and obesity which may be the presenting complaint lesser degrees of abnormality which properly call for attempts at correction are present in a large proportion of all patients

The starting point must always be the evaluation of the caloric status at the time Is the patient fat or thin? It is better to answer this question than to decided whether he is overweight or underweight according to the chart At the same time the presence of any abnormality of hydration should be considered, since this may confuse the issue of fatness or leanness Occult edema is troublesome, since it may represent a sizable part—up to around 10 per cent—of the mass of the body in undernourished persons [40], the thin skin and absence of fat pads in the usual places (abdomen, buttocks) usually reveal the true state Recent changes in body mass should be discovered from the history and the way in which the clothes fit

After the actual nutritional state has been evaluated the decision must be made as to whether it should be changed and if so how Perhaps it is desirable to keep the diabetic patient thin and the tuberculous patient fat Perhaps a good psychologic state in a patient can be maintained only with a generous caloric intake and perhaps this is more important than the extra hazard of circulatory disorder in the obese Such points arise but decisions must be made The basic requirements for the subsequent caloric prescription are simple but effective application may be extremely difficult because of the patient's attitude or complicating disease Except in hyperthyroid patients it is seldom wise to attempt the alteration of caloric balance by changing the energy output it is far easier and surer to adjust the intake In the great majority of cases patience and a clear understanding of the elementary facts of nutrition will suffice to bring success

40 Keys A Taylor H L. Mick lsen O and Hensch l A Famine Edema and th Mechan m of Its Format on Sc nc **103** 669 1946 Henschel A M ckelsen O Tayl r H L and Keys A Volume and Thiocyanate Sp ce in *Fam ne Edema and Recovery Am. J Phys ol.* **150** 170 1947

CHAPTER XIV

FEEDING OF HEALTHY INFANTS AND CHILDREN

PHILIP C JEANS

FEEDING OF INFANTS

Human milk is the ideal food for the young infant supplying all the nutritional essentials for the early period with the exception of vitamin D When human milk is not available, cow's milk is used in substitution These two foods have different contents of nutritional essentials and different effects on body composition Comparative contents are shown in tables 1 and 2

The breast-fed baby who is thriving receives from 2 to 2 5 Gm of protein for each kilogram of body weight In the feeding of cow s milk to the young infant it is common practice to supply at least 1½ ounces (44 ml) of milk for each pound of body weight This amount is equivalent to 100 ml for each kilogram and a protein intake of 3 4 Gm for each kilogram The larger protein intake of the artificially fed baby is reflected in a greater nitrogen content of the body This difference is shown in chart 1 After birth the percentage content of nitrogen of babies receiving cow s milk increases in a *curve rather smoothly continuous* with the curve of prenatal content[1] When human milk is fed a sharp change in the direction of the curve occurs after birth and for a time the proportion of nitrogen in the body remains at birth level or decreases slightly

The breast fed baby who is thriving receives approximately 0 06 Gm of calcium for each kilogram of body weight The artificially fed baby who ingests 100 ml of cow s milk for each kilogram receives 0 12 Gm of calcium for each kilogram The larger calcium intake of the artificially fed baby produces a greater calcium content of the body as shown in chart 2 With both types of feeding a decrease in percentage of calcium in

1 Stearns, G The Mineral Metabolism of Normal Infants, Phys ol. Rev 19:415 (July) 1939

relation to body weight occurs for several weeks after birth, after which period the percentage content with cow's milk feeding starts to rise, while that with human milk feeding continues to fall for several weeks and

TABLE 1—*Approximate Percentage Composition of Human Milk and Cow's Milk* *

Type of Milk	Fat	Sugar	Total Protein	Lactalbumin	Casein	Total Ash	Calcium	Magnesium
Human	3 5	7 5	1 [illegible]5	0 [illegible]	0.50	0 [illegible]0	0 03[illegible]	0 004
Cow s	3.5	4 7	3 4	0 50	3 0	0 [illegible]5	0 118	0 01[illegible]

Type of Milk	Potassium	Sodium	Phosphorus	Sulfur	Chloride	Iron	Copper
Human	0 041	0 011	0 013	0 014	0 0[illegible]	0 0001	0 00003
Cow s	0 1[illegible]	0 0[illegible]0	0 093	0 033	0 10[illegible]	0 00005	0 00002

The figures of this table are intended to represent mean values. For compiled ranges for some of these components reference may be made to Jeans P C and Marriott W M Infant Nutrition ed 4 St Louis C V Mosby Company 1947

TABLE 2—*Approximate Vitamin Content of Human and Cow's Milk*

Average Values for Each 100 Gm or Ml

Type of Milk	Vitamin A, I U	Vitamin D I U	Vitamin C Mg	Thiamine Mg	Riboflavin Mg	Niacin Mg
Human	[illegible]90	5 0	6 4	0 013	0 04	0 1
Cow s †						
Raw	180	2.5	2 0	0 04[illegible]	0 20	0 1
Pasteurized	180	2 5	1 1	0 035	0.20	0 1
Evaporated Reconstituted	180	2 5	0 6	0 025	0 20	0 1

Values for human milk are based on data from Macy I G Williams H H Pratt J P and Hamil B M Human Milk Studies Am J Dis Child 70 : 1 5 (Sept) 1945

† Values for cow s milk are based on data from Lawrence J M Herrington B L and Maynard L A. Human Milk Studies Am J Dis Child 70 193 (Sept) 1945.

probably does not reach the birth value before the baby is 1 year of age The calcium content of human milk is used more efficiently than that of cow s milk but the total retention from cow s milk is greater because of the larger quantity fed The calcium reten-

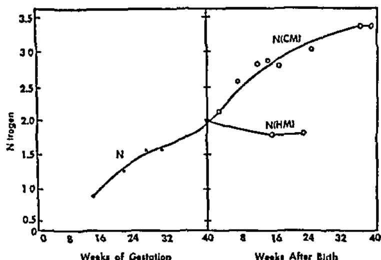


Chart 1 —Changes in relative nitrogen content of fetus and infant. The regression line of nitrogen content of the fetus is drawn from data n the l terature CM infants fed cow s m lk HM infants fed human m lk (From Stearns G Physiol. Rev 19 415 [July] 1939)

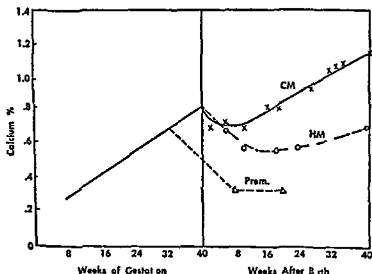


Chart 2 —Changes in relative calcium content of fetus and infant. The regression l ne of calcium content of fetus is drawn from d ta in the l te atu e. CM infants fed cow s milk HM infants fed human milk Prem prematurely born infants *fed human milk.* (*From* Stearns, G Physiol. Rev 19: 415 [July] 1939)

tion of the baby fed cow's milk is as great as or greater than the calcium intake of the breast fed baby

The significance of these differences in body composition is not clear One interpretation could be that a wide range of normal exists and that the differences are of no great significance The period of time during which the differences exist is short compared with the life span The differences disappear soon after the differences in diet cease to exist

While this point of view may be acceptable for the baby born at term, it is inappropriate for the baby born prematurely The chief reasons the prematurely born baby is highly susceptible to rickets are the low calcium and phosphorus content of the body at birth and the frequent failure to supply sufficient of these minerals after birth Human milk cannot be ingested in amounts sufficient to supply the need unless it is fortified or supplemented with calcium or a calcium containing food

In explanation of the high calcium content of the baby fed cow s milk as compared with the baby fed human milk, and with the justifiable concept that human milk is the ideal food the idea has been advanced that the baby fed cow s milk is supermineralized Eliot and Park [2] interpreted the results of their study of the bones of newborn babies as indicating that calcium is present in sufficient amount to represent storage This interpretation was accepted by Hamilton,[3] who expressed the belief that the relative calcium loss in early infancy represents utilization of stores and is normal After 3 months of age the rate of percentage of calcium increase in the body when cow s milk is fed parallels the fetal rate a condition which if it does not represent physiologic normal growth at least produces storage Storage to this extent certainly is not harmful and it may well be considered useful during periods of illness when calcium utilization is impaired The rate of calcium increase after 3

2 Eliot M M and Pa k E A Rickets in B ennenmann J System of Pediatrics Hagerstown Md. W F Pr or Company 1938 vol 1 chap 35

3 Ham lton B Calcium and Pho phorus Metabolism of Prematures, Acta pædiat. 2 1 1923

months of age for the baby fed cow's milk is similar to the rate of increase of ash content of the fat free animal body as predicted by Moulton[4]

Linear growth of babies fed a standardized cow's milk formula is related to the amount of calcium retained[5] The differing retentions with the standardized diet are obtained by varying the vitamin D intake Babies with poor retentions grow at average or less than average rates while those with higher retentions grow at rates greater than average Thus the higher calcium retentions would appear to be definitely advantageous to the artificially fed infant On the other hand, the breast fed baby has excellent linear growth despite a much lower calcium retention and grows at a rate definitely greater than that of the artificially fed baby who has the same calcium retention[6] It becomes obvious from these and other facts that factors other than those under consideration enter into the rate of growth and that probably it is inappropriate to state requirement standards for the artificially fed baby based on the requirement of the baby fed human milk

The greater nitrogen retention of the artificially fed baby must of necessity represent larger amounts of tissue protein in the body since nitrogen is not stored in any other fashion The larger part of the increase in tissue protein is represented in increase in muscle mass Babies who are fed cow's milk in the larger of the customary quantities have approximately 25 per cent more muscle mass than breast fed babies[7] This increase takes place soon after the artificial feeding is started after which time the muscle mass maintains a fairly constant relationship to the total body weight The muscle masses of breast fed and artificially fed babies increase in a parallel manner but with larger values for those receiving cow's milk No disadvantage seems to accrue to the breast fed baby because of the lesser amount of muscle On the other hand nitrogen

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4 Moulton C R Age and Chemical Development in Mammals J Biol. Chem 57:79 (Aug) 1923

5 Stearns G Jeans, P C and Vandecar V The Effect of Vitamin D on Linear Growth in Infancy J Pediat. 9 1 (July) 1936 Slyker F Hamil, B M Poole, M W Cooley, T B and Macy I G Relationship Between Vitamin D Intake and Linear Growth in Infants Proc. Soc. Exper Biol & Med. 37 499 (Dec.) 1937 Jeans and Stearns[20]

6 Jeans P C and Stearns, G Unpublished data.

7 Catherwood R, and Stearns G Creatine and Creatinine Excretion in Infancy J Biol. Chem. 119:201 (June) 1937

retentions of the artificially fed baby of the same order of magnitude as those of the breast fed baby are associated with poorer tissue turgor and poorer motor development than are shown by artificially fed babies receiving the larger amounts of cow s milk and having higher nitrogen retentions If these observations are correct, cow s milk formulas devised to simulate human milk in percentage composition are not so useful as are formulas containing larger amounts of protein and calcium

The phosphorus content of the body and the phosphorus requirement depend on the amounts of calcium and nitrogen retained Consequently the requirement of the baby receiving cow's milk is somewhat greater than that of the infant fed human milk The phosphorus content of human milk is much less than that of cow s milk but human milk contains an amount sufficient to meet the needs of the infant relative to the amounts of calcium and nitrogen retained Cow's milk contains an excess to the extent that much more phosphorus is absorbed than can be used the excess being excreted chiefly in the urine Little or no phosphorus is excreted in the urine of the breast fed baby whereas in the artificially fed baby 60 to 70 per cent of the total excretion is by way of the urine The baby seems to accomplish the increased excretion without difficulty or damage

Human milk is superior to cow s milk as a source of iron Although human milk contains only 0 5 to 1 5 mg of iron to the liter, it contains on the average twice as much as does cow s milk The iron stores at birth are sufficient to permit maintenance of a normal hemoglobin level for several months after which time additional iron is necessary After 3 months of age with customary cow s milk formulas the iron retention is variable but averages approximately zero, when human milk is fed the average retention is approximately 0 11 mg Neither of these iron intakes is satisfactory, for a retention of at least 0 7 mg is required after 6 months to maintain the hemoglobin level[8] Without additions the body of the baby becomes progressively poorer in iron The iron content of human milk and its utilization are such that nutritional anemia is much slower to develop in the breast fed baby than in the artificially

8 Stearns G and Stinger D Iron Retention n Infancy J Nutrition 13 127 (Feb) 1937

fed baby when no iron supplement is given Possibly also the greater content of folic acid in human milk plays a role

Whether the baby is breast or artificially fed, special supplements of vitamin A are unnecessary The requirement for vitamin A is related to body size The Food and Nutrition Board of the National Research Council has recommended 1 500 units daily at 6 months of age Even for a baby 1 year of age this amount is greater than that computed as optimum on the basis of weight from experiments with animals when all the vitamin A is ingested as carotene Thus the amount recommended appears ample Computation shows that the required amount of vitamin A is supplied by milk alone, either human [9] or bovine [10] if it is of average content In the early months the breast-fed baby receives more vitamin A than does the baby fed a cow's milk formula prepared by dilution In addition to the vitamin A of the milk the early addition of orange juice makes a small contribution and the subsequent additions of egg yolk vegetables and fruits permit an intake of vitamin A or its precursors well above the recommended allowance Clinical observations also have shown that babies receiving a normal standard diet grow equally well whether or not they receive additional vitamin A [11] Thus for the average baby the important contribution of fish liver oil is vitamin D

The ascorbic acid content of human milk varies directly with the intake of the mother [1] but in general is relatively large in comparison with the content of prepared cow s milk An approximate average content of human milk in this country is 50 mg to the liter, whereas a cow s milk formula prepared by boiling and

9 F derichsen C and With T K Ueber den Gehalt der Frauen milch an Karotinoiden und A Vitamin besonders in bezug auf *seine* Abhangigkeit von der Kost, Ann. pæd at. **103** 113 (June) 1939 Dann, W J The Transm ssion of Vitam n A from Parents to Young in Mammals V The V tamin A and Carotenoid Contents of *Human* Colostrum nd Milk, B ochem J **34**:724 (May) 1940

10 Dornbu h A C Peterson W H, and Olson F R The Carot ne and V tamin A Content of Market Milks, J A M A *114 1748* (May 9) 1940 Tech Bull. no. 802 United States Department of Ag iculture December 1941

11 Lew s J M and Barenberg L H The Relationship of V tamin A to the He lth of Infants J A M A **110** 1338 (April 23) 1938 Jeans and Stearns [1a]

12 Selleg I and King C. G The Vitamin C Content of Human Milk and Its Var at on with Diet, J Nutrition **11** 599 (June) *1936* Winkler H and Heins E. Der Askorbinsauregehalt d r Frauenmilch im Sommer und Winter Ztschr f Geburtsh. u. Gynak **117**:148, 1938

dilution may contain 6 mg or less to the day's supply[11] Thus average human milk meets the standard allowance for vitamin C, whereas the amount in prepared cow s milk is grossly inadequate Even though the requirement is met by average human milk the feeding of orange juice to the breast fed baby is in no way harm ful and may be considered beneficial in those instances in which the mother s supply of ascorbic acid is small

The thiamine content of human milk varies widely and depends on the diet of the mother[14] Knott and her co workers[15] found that milk from mothers who supply their infants adequately contains more thiamine than milk from mothers whose babies require a formula supplement When mothers supplied their babies adequately the milk contained an average of 192 micro grams to the quart, with inadequate supply the average content was 86 micrograms The larger of these two values was obtained when the mothers received approximately 1 5 mg of thiamine daily At times the thiamine content of human milk is less than the require ment of the infant Clements[16] observed symptoms of partial thiamine deficiency in 8 per cent of a group of 150 breast-fed babies The thiamine content of the milk was low in each case

Cow s milk as fed to babies is subjected to heat treat ment, which causes significant losses of thiamine as compared with the original milk Table 2 shows that

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13 Holmes A D Tripp F, Woelffer E. A and Satterfield, G H Ascorbic Acid Content of Cow's M lk at Various Stages of Lactation, Am J Dis Child. 60 1025 (Nov) 1940 Riddell W H Whitnah, C H Hughes J S and L enhardt H F Influence of the Ration on the V tam n C Content of Milks Raw Pasteurized and Baby Formulae, J Am Dietet A 14 275 (April) 1938 Trout, G M., and Gjessing E C Ascorbic Acid and Oxid zed Flavor in M lk I Distribution of Ascorb c Acid and Occu rence of Oxidized Flavor in Commercial Grade A Raw in Pasteuri ed Irrad ated and in Pasteurized Milk Throughout the Year J Dairy Sc. 22 271 1939 Holmes, A D Tripp F Woelffer E. A. and Satterfield G H The Influence of Pasteurization on the Asco bic Acid (V tam n C) Content of Certified Milk J Am. Dietet. A 15 363 (May) 1939 Rasmussen R. Guerrant, N B Shaw A O Welch R C Effects of B eed Cha act ristics a d Stages of Lactation on Vitam n C (A co b c Acid) Content of Cow s M lk J Nut ition 11 425 (May) 1936

14 Mo gan A F and Hayne E G V tamin B Content of Human Milk as Affected by Ingestion of Thiam ne Chlo de J Nutrition 18 105 (Aug) 1939 Slat r E C and Rial E J The Thiamin (V tam n B) in Hum n Milk M J Australia 1 3 (Jan 3) 1942 W denbauer F and Heckler F Ueb den Vitamin B_1 G halt der Kuh und F auenm lch Ztschr f Kinde h. 60 683 1939 Kendall N Thiam ne Content of Var ous M lks J I ed at. 20:65 (Jan) 1942 Knott, Kleiger and Bracamonte[15]

15 Knott E M Kle ge S C and Bracamonte F T Factors Affecting the Thiam n Content of Breast Milk J Nutr tion 25 49 (Jan) 1943

16 Clements F W The Symptoms of Partial V tam n B_1 Deficiency in Breast Fed Infants M J Australia 1 12 (Jan. 3) 1942

heat treated cow s milk contains more thiamine than does human milk However cow s milk usually is diluted for feeding the young baby Even with maximum customary dilution the thiamine intake of the artificially fed baby equals or exceeds that of the breast-fed baby when averages are considered

The minimum thiamine requirement is approximately *0 24 mg for each 1 000 calories*[17] *Symptoms of* deficiency do not appear when this amount is ingested The thiamine intake should be something more than the minimum requirement The allowance considered appropriate by the Food and Nutrition Board of the National Research Council is 0 5 mg for each 1,000 calories or 0 4 mg daily for a baby 6 months of age Both average human milk and average dilution formulas for young infants contain only the minimum requirement of thiamine Thus questions have arisen as to the adequacy of the thiamine intake of the infant The breast fed infant although he has no thiamine to spare, seems to do very well nutritionally One difference *between human milk and formulas of cow's milk is the* higher proportion of calories from fat in human milk Slightly more than 50 per cent of the calories of human milk are from fat while the calories from fat in a customary formula often are as low as 35 per cent. Thiamine is not concerned in fat metabolism and fat consequently has a sparing action on thiamine Therefore the thiamine requirement is more equally met in the two instances *than seems apparent In any case* early supplement with thiamine-containing foods is desirable

With prevention of depletion of body stores as determined by load tests used as the criterion for the riboflavin requirement approximately 20 micrograms for each kilogram is the minimum requirement for adults[17] The allowance recommended for adults by *the Food and Nutrition Board of the National* Research Council is one third more than this minimum requirement or 26 micrograms for each kilogram Requirement data for children and particularly for infants are meager Some implication exists that infants and children may need relatively more than do

17 Recommended Dietary Allowances revised 1948 National Research Council Reprint and Circular Series no. 129

adults The Food and Nutrition Board has suggested an allowance of 75 micrograms for each kilogram for the infant, an amount probably higher than it need be

The riboflavin content of milk depends chiefly on the dietary intake It varies widely in human milk[18] and to a lesser extent in cow's milk[19] The average content of cow's milk is approximately five times that of human milk The young baby who receives practically all his food as human milk gets approximately 65 micrograms of riboflavin for each kilogram The young baby who receives a customary dilution formula receives at least 160 micrograms for each kilogram Thus the riboflavin intake of babies receiving cow's milk formulas need cause no concern, and it is probable that the intake of the thriving breast fed baby is ample even though it does not meet fully the suggested allowance of the Food and Nutrition Board

Niacin requirement is directly related to the protein intake at all ages inasmuch as part of this requirement can be supplied by tryptophan When the tryptophan content of the diet is low the niacin need is approximately 10 times that for thiamine on this basis a suitable allowance at 6 months is approximately 4 mg and the minimum requirement half this amount At this age the infant obtains 1 to 2 mg daily from his milk[20] and relatively little from other food sources The reason that deficiency symptoms do not occur with a customary diet is that milk is a good source of tryptophan Both tryptophan and niacin are necessary for growth

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18 Neuweiler W Ueber den Flavingehalt der Frauenmilch Klin Wchnschr **16** 1348 (Sept 25) 1937 Muller R Beobachtung uber dem Lacto-flavingehalt der Frauenmilch und seine beeinflussung durch die Ernahrung Klin Wchnsch **16** 807 (June 5) 1937

19 Henry K M Houston J and Kon S K Estimation of Riboflavin II The Estimation of Riboflavin in Milk Comparison of Fluorimetric and Biological Tests, Biochem J **34** 607 (April) 1940 Johnson P Maynard L A and Loosli J K The Riboflavin Content of Milk as Influenced by Diet J Dairy Sc **24** 57 1941 Clouse R C III Essentials of an Adequate Diet, Hygeia **19**: 817 (Oct.) 1941 Teply Strong and Elvehjem[20]

20 Kodicek E Estimation of Nicotinic Acid in Animal Tissues Blood and Certain Foodstuffs II Applications Biochem J **34** 724 (May) 1940 Teply L J Strong F M and Elvehjem C A. The Distribution of Nicotinic Acid in Foods J Nutrition **23** 417 (April) 1942 Bailey E A Jr Dann W J Satterfield G H and Grinnells C D A Method for the Estimation of Nicotinic Acid in Milk J Dairy Sc **24** 1047 1941 Noll C I and Jensen O G The Chemical Determination of Nicotinic Acid in Milk J Biol Chem **140** 755 (Sept.) 1941 Snell, E. E and Wright L. D A Microbiological Method for the Determination of Nicotinic Acid ibid **139**: 675 (June) 1941

Neither human[21] nor cow's milk[22] supplies an important amount of vitamin D The various relationships of the components of human milk, including the calcium to phosphorus ratio are such that calcium and phosphorus are more efficiently utilized from this food than from cow's milk Rickets is less common among breast fed than among artificially fed babies Nevertheless breast fed babies sometimes develop rickets, and the calcium and phosphorus retentions of babies receiving human milk are increased when vitamin D is given The requirement of the breast fed baby for vitamin D is not known accurately but probably it is little or no different from that of the artificially fed baby as discussed subsequently

In the preceding discussion certain large differences in body composition between breast fed and artificially fed babies have been mentioned The significance of these differences to the baby is not clear Our present knowledge does not seem to warrant the selection of one type of composition as preferable to the others Detailed nutritional studies have not proved any inferiority of human milk as compared with cow's milk in infant feeding despite the facts that certain essential components are present in small amount and that well managed artificial feeding produces a type of body composition that might seem more desirable from certain theoretical points of view The usual reasons advanced for preference for feeding human milk are trite although largely correct These reasons pertain to ease of digestion low bacterial count, relative freedom of the infant from infection infrequency of digestive disturbances production of good growth and physical status infrequency of serious illness relative ease of diet regulation relative absence of allergy avoidance of human error in prescribing and preparing a formula and psychologic satisfaction It may be as so often is stated that nature intended human milk for the human infant and cow's milk for the more robust stomach and more rapid growth of the calf However nature has not informed us so clearly as to when other foods should be added to the diet and what foods should be given For answers to these questions

21 Drummond J C Gray C H and Richardson, N E G Antirachitic Value of Human Milk Brit M J 2 757 (Oct 14) 1939

22 Bechtel H E and Hoppert C A Seasonal Variation of the Vitamin D in Normal Cow Milk, J Nutrition 11 537 (June) 1936

we must depend on empiric practice as modified from time to time by scientific observation That certain food components should be added early seems clear

Supplements to the Milk Diet of the Infant—Ascorbic Acid Most babies at birth have blood levels of ascorbic acid of at least 0 7 mg and some 1 0 mg or more for each 100 ml of blood [3] The blood level decreases promptly and rapidly By the tenth day the artificially fed baby may be expected to have approximately 0 4 mg for each 100 ml of blood, an undesirably low level By the fourth or fifth day the breast fed baby is receiving ascorbic acid in significant amounts, but in the case of the artificially fed baby the custom of delaying vitamin C administration until the second month is altogether too common Orange juice the most frequently used source even when started late, is commonly given in amounts much too small to meet the need The young artificially fed baby has been found to need approximately 20 mg of ascorbic acid daily in addition to the small amount in the formula in order to have a blood value comparable to the lower blood levels of breast-fed babies Thus at least an ounce (30 ml) of orange juice is desirable, beginning in the early days after birth By the time the baby is 3 months old the amount of orange juice given could well be 2 ounces (60 ml) or even more 2 ounces supply approximately 30 mg of ascorbic acid a suitable allowance for this age period In the private practice of medicine intolerance of orange juice is encountered frequently, but in hospital practice this condition is found most rarely From the point of view of digestion orange juice is little more than a 10 per cent solution of glucose a food that should not disturb the alimentary tract of the most delicate infant Perhaps it is not a coincidence that babies who cannot tolerate orange juice also have difficulty with tomato juice For those who are intolerant to these foods ascorbic acid is widely available

The prematurely born baby has a need for ascorbic acid greater than that of the baby born at term vitamin

3 Braestrup P W The Content of Reduced Ascorbic Acid in Blood Plasma in Infants Especially at Birth and in the First Days of Life J Nutrition **16** 363 (Oct) 1938 Mindlin R L The Relation Between Plasma Ascorbic Acid Concentration and Diet in the Newborn Infant J Pediat. **13** 309 (Sept.) 1938

C is necessary for utilization of several of the essential amino acids [24] The amount usually adequate for this purpose is 50 mg

Vitamin D The need for vitamin D from special sources exists from birth One good argument favoring the use of milk fortified with vitamin D is that probably no one hesitates to prescribe this type of milk for the earliest formulas, whereas perhaps the majority of physicians wait several weeks or into the second month before prescribing a fish liver oil Fish liver oils in appropriate amounts may be expected to produce no digestive difficulties at 1 to 2 weeks of age The condition to be feared most at this early age is lipoid pneumonia produced by aspiration of the oil It is partly for this reason that some physicians use concentrated preparations of vitamin D in preference to cod liver oil Other and perhaps preferable alternatives exist Preparations of both vitamin D_2 and D_3 are commercially available in solutions that are freely miscible with the milk formula and offer the advantage of dispersion of the vitamin in which state it is more efficiently utilized than in the concentrated form

The requirement for vitamin D has been set at 400 units daily by the Food and Drug Administration, 400 units is the daily allowance recommended by the Food and Nutrition Board of the National Research Council No acceptable evidence has been found that a normal infant needs more than 350 units daily for optimum or for maximum calcium utilization when the vitamin D is of no greater concentration than exists in cod liver oil [25] The prescribing of several times this amount is common practice Evidence exists that amounts greater than 1 500 units daily are detrimental in that appetite decreases after several months of use with consequent decrease in calcium retention and in growth rate [26] One teaspoonful daily of the less potent of the

24 Levine S Z Marples E. and Gordon, H H A Defect in Metabolism of Tyrosin and Phenylalanine in Premature Infants I Identification and Assay of Intermediary Products, J Clin Investigation **20**: 199 (March) 1941 II Spontaneous Occurrence and Eradication by Vitamin C ibid. **20** 09 (March) 1941 Denn, M. The Influence of Diet on the Ascorbic Acid Requirement of Premature Infants, J Clin. Investigation **21** 139 (Jan) 1942

25 Jeans P C and Stearns, G The Human Requirement of Vitamin D J A. M A **111** 703 (Aug 0) 1938 reprinted in The Vitamins, a symposium, Chicago American Medical Association, 1939 chap. 26 pp 483 51

26 Jeans P C., and Stearns, G The Effect of Vitamin D on Linear Growth in Infancy II The Effect of Intakes Above 1 800 U S P Units Daily J Pediat. **13** 730 (Nov) 1938

acceptable cod liver oils or ½ teaspoonful of the highly potent cod liver oils is adequate If preparations of such concentration as viosterol are used, a dosage of 4 or 5 drops is preferable to the 10 drops so commonly used The dosage of vitamin D should be considered in terms of units, volumes should be stated only in interpretation to the caretaker of the infant in relation to the specific product to be used

The concept is widely held that the baby born prematurely requires more vitamin D than does the baby born at term This concept seems to be in error [27] The increased susceptibility of the prematurely born baby to rickets is due to needs for larger intakes of calcium and phosphorus than often are supplied The vitamin D requirement is not increased

Cereals It is the almost universal custom in this country to prescribe cereal as the baby's 'first solid food' The age at which cereal is given to infants has varied with different generations of physicians, but at present addition of cereal to the diet at 3 months is common practice This current practice finds its counterpart in ancient times and is an empiric custom Its continuance has been based on the clinical impression and belief that babies thrive better when receiving cereal Among the cereal products often listed as suitable for infant feeding are farina preparations, foods that presumably add little to the nutritional value of the infant's diet

Earlier in this review has been mentioned the usefulness of supplementing the milk diet of the infant with foods containing iron and thiamine and possibly other members of the B complex Whole grain cereals and especially fortified proprietary cereal foods contribute importantly to the satisfaction of these needs Thus an empiric custom receives support from modern scientific evidence but only when cereal foods are carefully selected

It is the custom of a few physicians to defer the feeding of cereals until the second half of the first year and to supply the needed iron and B vitamins from egg yolk, vegetables and fruits When these foods are given in appropriate quantities the supply of iron and the B vitamins is somewhat greater than from whole grain

27 Glaser, K Parmelee A H and Hoffman W S Comparative Efficacy of Vitamin D Preparations in Prophylactic Treatment of Premature Infants Am J Dis Child 77:1 (Jan) 1949

cereals, although not greater than from some of the fortified proprietary foods. Thus among the natural foods the known needs of the infant are supplied better from egg yolk, vegetables and fruits than from whole grain cereals. When these foods are given, the feeding of cereal loses much of its importance and may be deferred until the capacity of the infant increases to the extent that the entire group of foods can be taken comfortably.

Other Supplementary Foods. Some of the food values of egg yolk, vegetables and fruits have been mentioned in the preceding section. Egg yolk is frequently given, preferably cooked, at 3 to 4 months of age, sieved vegetables at 4 to 5 months and sieved fruits at 4 to 6 months. The giving of a variety of these foods twice a day instead of the usual cereal twice a day not only supplies needed nutrients but helps to accustom the infant to variety in flavors and textures of foods, a goal highly desirable from the point of view of forming good feeding habits.

Meat. Meat preparations excellent for infant feeding are widely available in both sieved and coarser forms. If desired, the sieved meats can be fed at an early age. While meat protein is not an important addition to the milk diet, the meats are good sources of iron and the B vitamins; they are useful also in helping to give variety to the diet in texture and flavor.

Psychology of Infant Feeding.—The psychologic aspects of infant feeding[28] are fully as important as those more obviously nutritional. One of the common complaints relating to children brought to the pediatrician is anorexia, usually dependent on training in feeding habits and usually having its origin in infancy. Often the formula prescription of the physician contributes to the onset of the difficulty. A definite volume of food is prescribed and the conscientious and solicitous parent endeavors to give this exact quantity of formula at each feeding regardless of possible variations in appetite. In this manner rebellion against food and the parent may have its beginning.

The interrelationships which are set up between mother and child during the early days and weeks after birth set a pattern which is important in

28 Bakwin, R. M., and Bakwin, H.: Psychological Care of the Preschool Child (pt. 1), J. Pediat. 16: 89 (Jan.) 1940; (pt. 2) ibid. 16: 220 (Feb.) 1940. Aldrich, C. A., and Aldrich, M. M.: Babies Are Human Beings, New York, The Macmillan Company, 1947.

determining the type of response the child will have toward eating Giving and receiving represent the most basic aspect of all social relationships The infant mother relationship is the simplest example of a social situation Attitudes are communicated to the infant from the earliest moments and affect his behavior The perception of impatience or hostility by the infant heightens the anxiety in him and produces physiologic changes which are not conducive to satisfactory feeding and digestion Changes in the type of food or manner in which it is given constitute a problem in learning for the infant Hence psychologic preparedness for changes should be evaluated by assessment of the infant's mood

Feeding by both parents is helpful in fostering emotional development. The mother needs the active support of her husband and the doctor The infant's manual preparedness in feeding develops after 6 or 7 months and should be encouraged so far as is feasible

Acceptance or rejection of new foods is affected greatly by the attitude of the mother toward those foods If a mother has a revulsion toward a food such as cod liver oil for example, communication to the baby of her emotional state is common, with the result that the baby refuses the food The baby's behavior is modified by the unconscious attitude of the mother Correction of this fault is difficult

The so-called self demand schedule has become fairly common Much is to be said in favor of having the baby's feeding time when he is most frequently hungry rather than at some time regulated by the clock. Usually such a schedule is regulated by the mother rather than by the doctor and some common sense is required Thus the schedule is easily subject to abuse and the baby may be fed every time he cries, a procedure that leads to faulty feeding habits

The desirability of variety in flavor and texture has been mentioned These variations should be introduced early The child who has had only liquid and sieved foods throughout the first year frequently refuses coarser foods when finally they are offered At least some of the fruits and vegetables offered should be chopped or mashed rather than sieved after the sixth or seventh month The continuance of bottle feeding after the first year is not good feeding practice and is usually evidence that other environmental factors are faulty

FEEDING OF CHILDREN

The conclusion is reached easily that the diets of our children have improved in many ways over those of the past It is clear also that they have not yet improved sufficiently even in those economic levels at which the cost of food is relatively unimportant

It is customary to attribute increased rate of growth of a population group to improvement in nutrition Certainly it has been demonstrated that nutrition definitely affects the rate of growth Whether the cause is wholly nutritional or dependent also on greater freedom from disease and on other factors studies have shown that young people of this country are taller and heavier than were the children of former years For example Meredith [29] has shown that boys living in the United States today are 6 to 8 per cent taller and 12 to 15 per cent heavier than was the case half a century ago He found the size of the boys to be related to economic status He found also that differences in size were unimportant when related to geographic distribution within the United States

Other studies have shown that well fed babies and children grow at rates greater than average Growth rates of babies recorded over the past 25 years show a gradual and definite increase starting with the data of Baldwin (1921) [30] and progressing through those of Kornfeld (1929) [31] Stuart (1934) [32] and Jackson (1945) [33] Although these differences are greater among infants they appear also for the child The assumption seems justified that the increased growth rates are largely attributable to improved nutrition

Despite improvement in nutrition over the years, much evidence exists that current diets are often unsatisfactory While the national over-all averages of per capita consumption of food show no deficiency dietary surveys in families show an unequal distribution of food and nutritional essentials [34] The nutrients most

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29 Meredith H V Stature and Weight of Children of the United States Am. J Dis. Child 62 909 (Nov) 1941

30 Baldwin B T The Physical Growth of Children from Birth to Maturity *Iowa City University of Iowa, 1921 no. 1*

31 Kornfeld W Zur Bewertung von Grosse und Gewicht bei Knaben und Madchen aller Altestufen, Ztschr f Kinderh. 48 188 1929

32 Stuart, H C. Standards of Physical Development for Reference in Clinical Appraisement Suggestions for Their Presentation and Use, J Pediat. 5 194 (Aug) 1934

33 Jackson, R. L. and Kelly H G Growth Charts for Use in Pediatrics Practice J Pediat. 27: 215 (Sept.) 1945

34 Nutrition Surveys Their Techniques and Values, National Research Council Bulletin no. 117 (May) 1949 p. 37

commonly found deficient are riboflavin, calcium, thiamine and ascorbic acid Although not often mentioned in this grouping, protein and vitamin D deficiencies also are relatively common in childhood These deficiencies are discussed subsequently

Another dietary fault is represented in the occurrence of dental caries While no consensus exists as to the details of the cause of dental caries or the mechanism of its prevention, whether it is nutritional or oral environmental, or both, it is generally agreed that diet plays an important role On this basis improper diet is common in childhood, since dental caries is almost universal

Except for special therapeutic purposes probably no need exists for special preparations of vitamin A to be given in addition to that present in the diet Evidence is conflicting concerning the frequency of vitamin A deficiency among the children of this country Certainly vitamin A is relatively abundant in many of our foods and any reasonably good diet contains ample not only to meet the minimum requirement but for storage It is clear also that if a diet is fortuitously deficient in vitamin A it is deficient also in many other essentials and that much more is needed than the addition of vitamin A alone It is believed that in a high proportion of instances in which children are found to have clinical evidence of vitamin A deficiency the deficiency is dependent on defects of utilization in greater measure than on dietary deficiency[35] Infections and illnesses produce prompt response in impairment of utilization In the continued presence of illness large therapeutic doses of vitamin A may be required to supply the need or these large doses may fail to produce a noticeable effect

Vitamin D is commonly deficient in the diet of the child Many children receive an inadequate amount of sunshine in the summer and few receive a sufficient amount in winter Giving vitamin D preparations has become routine in infancy but relatively few mothers realize that vitamin D is important throughout the growth period Without vitamin D children vary widely in their ability to use calcium and phosphorus for some the utilization is excellent for others poor Since distinction between these two types of children cannot be made without prolonged and detailed special

35 Jeans P C. Blanchard E L and Satterthwaite F E. Dark Adaptation and Vitamin A, J Pediat. 18 170 (Feb) 1941

study for each child, it is appropriate to consider that all children require vitamin D When the calcium and phosphorus intakes are adequate and appropriate, 300 to 400 units of vitamin D daily will produce retentions of these minerals ample to satisfy the theoretical requirements for normal growth

Much circumstantial evidence exists that thiamine probably is obtained by many children in amounts less than those considered appropriate or optimum[36] The remedy for this situation, to the extent that it exists lies in a better selection of dietary components rather than in the giving of special preparations of thiamine In general refined cereal preparations are to be avoided except as they have been enriched The lower the economic level the greater the extent to which the energy need is supplied by refined cereal products and sugar, sometimes amounting to 50 per cent or more of the total energy intake Enriched bread and flour are now generally available Much ado has been made over the increasing consumption of refined sugar some believing that sugar is harmful per se but all agreeing that it is likely to replace foods more valuable nutritionally Macy[37] has observed that the better the diet from the nutritional point of view the less the desire of the child for sugar She concluded that the amount of sugar taken voluntarily by a child is an excellent criterion of the adequacy of the diet If this point of view is correct the point of attack is not to restrict sugar but to improve the diet by increasing the amounts of nutritionally valuable foods offered

Thiamine is reputed for its effect on the appetite An important proportion of children for whom parents seek medical advice are brought to the physician because of anorexia In few of these instances the anorexia is correctible by thiamine medication Although the child may be receiving suboptimal amounts of thiamine and

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36 Wilson H E C Pyruvic Acid Test for Thiamine Deficiency in Children Lancet 1 199 (Feb 14) 1942 Mason, H L and Williams, R D The Urinary Excretion of Thiamine As an Index of the Nutritional Level Assessment of the Value of a Test Dose J Clin Investigation 21 247 (March) 194 Wortis H Goodhart, R S and Bueding E. Cocarboxylase Pyruvic Acid and Bisulfit Binding Substances in Children Am. J Dis Child 61: 226 (Feb) 1941 Schlutz, F W and Knott E. M Cocarboxylase Content of Blood of Infants and of Children, ibid 61 231 (Feb.) 1941 Melnick, D Vitamin B_1 (Thiamine) Requirement of Man J Nutrition 24: 139 (Aug) 1942 Lane, R L Johnson E and Williams R R Studies of the Average American Diet I Thiamin Content ibid. 23 613 (June) 1942

37 Macy I C Nutrition and Chemical Growth in Childhood Evaluation in Springfield Ill. Charles C Thomas Publisher 1942 vol. I pp 84-85

other essentials, the fundamental difficulty lies in the environment and training in feeding habits, these bad habits often having had their origin early in infancy The correction of these habits has little relationship to thiamine

A child who ingests his expected allowance of milk receives from this source alone most if not all of the riboflavin required For the child who does not receive his quota of milk the possibility of deficiency not only of riboflavin but of other essentials as well is to be considered, and the diet must be supplemented accordingly in a special and expert manner if it is to be complete Meat, particularly the glandular organs and lean pork, is a good source of the B group of vitamins If ingested regularly, it is a better source of thiamine and niacin than is milk, it is inferior to milk as a source of riboflavin Eggs contribute importantly to the supply of B vitamins as well as other nutritional essentials and should be included in the diet frequently, preferably daily

Calcium is the chief mineral requiring attention during childhood since the other essential minerals are more likely to be present in sufficient amounts in most diets Milk and milk products are our best food source of calcium In the case of the young child the usual diet exclusive of milk contains approximately 0 2 Gm of calcium the diet of the older child contains approximately 0 3 Gm The remainder of the requirement of 1 to 1 5 Gm is normally supplied by milk Thus one may speak of the milk requirement in relation to the calcium need

A curve of the theoretical requirement for retention of calcium may be constructed by apportioning according to the rates of growth at different ages the total accretion of calcium from birth to maturity When such a curve is constructed the daily retention requirement is found to decrease from approximately 300 mg in infancy to a low point of about 180 mg early in the preschool period, then to increase to about 450 mg at the beginning of adolescence [38] The efficiency of children in calcium utilization varies widely but when vitamin D is given the range of retention is not great although always the amount ingested exceeds greatly the amount retained With respect to the calcium requirement in terms of milk it has been found that

38. Jeans P C and Stearns G Unpublished data

during the early part of the preschool period 1 pint (473 ml) of milk in addition to the usual diet permits *retentions adequate to meet the theoretical retention* requirement, which is low at this age[39] Very quickly after this time and up to approximately 10 years of age the retention requirement is not met until the quantity of milk is increased to 1½ pints (710 ml) daily The requirement during early adolescence is a quart (946 ml) of milk daily It seems unwise to place any emphasis on the low requirement in the early preschool period This period is brief approximately from 2 to 5 years of age *More is received by the baby immediately preceding this period and more is required* subsequently Milk should not be considered solely as a source of calcium It contributes most importantly to the requirement for protein as well as other essentials During the period when the calcium requirement is lowest the requirement for protein is high Consequently it seems preferable to advise at least 1½ pints of milk after the period of infancy and up to the age of 10 years *The taking of a full quart throughout* this period can be considered only as beneficial, provided the larger quantity does not crowd from the diet other essential foods The fear or belief that the larger quantity may have this effect is widely prevalent but not too well founded especially for those children who have normal appetites It is true that in some instances psychologic reasons arise for giving the smaller quantities of milk mentioned as meeting the calcium requirement *In such instances the protein requirement can* be met with other protein foods such as meat and eggs

Calcium deficiency at least in moderate degree is believed to be widely prevalent in childhood To whatever degree such a situation exists it is usually much worse during adolescence At this age period the requirement is increased and too often the intake not only is not increased but actually is decreased, sometimes because of a desire especially in girls to remain *slim It is during the adolescent period particularly* that dental caries tends to become rampant a condition

39 Daniels A L Hutton M K Knott E M Everson, C and Wright, O E Relation of Ingestion of Milk to Calcium Metabolism in Children Am J Dis Child **47** 499 (March) 1934 Daniels, A L Hutton M K Knott, E M Wright, O E and Forman M Calcium and Phosphorus Needs of Preschool Children J Nutrition **10**: 373 (Oct) 1935 Outhouse J Kinsman G Sheldon D Twomey I Smith J, and Mitchell H H The Calcium Requirements of Five Preschool Girls, ibid **17**: 199 (March) 1939

believed by many observers to depend in part on nutrition and by some observers to depend to some extent on calcium metabolism

The custom of prescribing or using calcium salts is widely prevalent Such salts have a definite field of usefulness in special circumstances, but they have no rightful place in the normal diet When they are used they should be chosen carefully for the purpose intended and the dosage should be more nearly adequate than it frequently is The phosphates of calcium are as well utilized as the same salts in milk The calcium needs for growth can be satisfied easily by means of these preparations In order that calcium may be usable for growth it is necessary that a proportionate amount of phosphorus be available at the same time The calcium of such salts as calcium lactate and gluconate is utilizable for retention only to the extent that phosphorus is present otherwise in the diet All diets contain at least a fair amount of phosphorus but the amount usually is not adequate to permit the best use of the calcium of these salts The chief objection to the customary use of the calcium salts is that they are not food in the usual sense, and they are often used as a substitute for milk It is obvious that calcium salts can be a substitute for milk in only a most restricted sense and that the diet must be supplemented in many additional ways in order to compensate for the absence of *milk*

The possibility of protein deficiency in the diets of children has received some but insufficient attention One of the criteria which may be used for estimating the protein content of the body is the creatinine output in the urine Creatinine excretion is directly proportional to the amount of muscle in the body [40] When children are fed ample protein the creatinine excretion (consequently the amount of muscle) rises to a constant level for each child with a narrow range at each age period for a group of children [41] When these values are plotted according to the age and in terms of creatinine for each kilogram of body weight a curve is obtained which may be considered as representing normal conditions as regards creatinine output and muscle mass Creatinine data collected from the literature as well as data from this clinic show that the great majority of

40 Hunter A C eatine and Creatin ne London Longmans Green & Co Ltd 19 8

41 Stearns G and others Unpublished data.

children studied have creatinine values below, often considerably below, the theoretically normal curve when they first come under observation Those with normal values are the exception rather than the rule In all the instances in which observations have been made the creatinine output increases promptly to the normal level when amounts of protein are fed which are consistent with what are considered standard dietary allowances It appears that when children receive suboptimum amounts of protein they approach as nearly to the normal creatinine excretion as their protein intakes permit them It is of interest also that the weight of the child may be and in fact usually is within what is considered the normal range when the low creatinine values are observed The size or weight of the body is not a criterion for judging protein metabolism

In meeting the protein requirement one should place emphasis on the value of milk A quart of milk daily supplies most of the protein need of the young child and half the need at the beginning of adolescence Such a quantity of milk contributes more protein to the diet than any other single food When milk is excluded from the diet the protein requirement of the child can be met only if special and expert supervision is given

SUMMARY

Despite all our modern knowledge of infant nutrition and all the current refinements of artificial feeding feeding at the breast of the mother remains an ideal procedure This is true despite the fact that human milk contains only a bare minimum of most of the nutritional essentials and the fact that the body composition of the breast fed baby departs widely from that which preceded and that which follows in contrast to the body composition of the artificially fed baby which maintains more closely a smooth continuance of the fetal and postinfancy curve

Vitamin D is needed early by all babies whether breast or artificially fed Vitamin C is needed early by artificially fed babies and is a harmless safeguard for the breast fed baby Babies born prematurely have a need for vitamin C somewhat greater than that of babies born at term and this need exists from the time of birth No need for vitamin A from special sources exists If current custom is in error it errs in the direction of giving too much vitamin D and too little vitamin C and in not giving either of these early enough

believed by many observers to depend in part on nutrition and by some observers to depend to some extent on calcium metabolism

The custom of prescribing or using calcium salts is widely prevalent. Such salts have a definite field of usefulness in special circumstances, but they have no rightful place in the normal diet. When they are used they should be chosen carefully for the purpose intended and the dosage should be more nearly adequate than it frequently is. The phosphates of calcium are as well utilized as the same salts in milk. The calcium needs for growth can be satisfied easily by means of these preparations. In order that calcium may be usable for growth, it is necessary that a proportionate amount of phosphorus be available at the same time. The calcium of such salts as calcium lactate and gluconate is utilizable for retention only to the extent that phosphorus is present otherwise in the diet. All diets contain at least a fair amount of phosphorus but the amount usually is not adequate to permit the best use of the calcium of these salts. The chief objection to the customary use of the calcium salts is that they are not food in the usual sense and they are often used as a substitute for milk. It is obvious that calcium salts can be a substitute for milk in only a most restricted sense and that the diet must be supplemented in many additional ways in order to compensate for the absence of milk.

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40 Hunter A. Creatine and Creatinine London Longmans Green & Co Ltd 1928

41 Stearns G and others Unpublished data

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In meeting the protein requirement one should place emphasis on the value of milk. A quart of milk daily supplies most of the protein need of the young child and half the need at the beginning of adolescence. Such a quantity of milk contributes more protein to the diet than any other single food. When milk is excluded from the diet the protein requirement of the child can be met only if special and expert supervision is given.

SUMMARY

Despite all our modern knowledge of infant nutrition and all the current refinements of artificial feeding, feeding at the breast of the mother remains an ideal procedure. This is true despite the fact that human milk contains only a bare minimum of most of the nutritional essentials and the fact that the body composition of the breast fed baby departs widely from that which preceded and that which follows, in contrast to the body composition of the artificially fed baby, which maintains more closely a smooth continuance of the fetal and postinfancy curve.

Vitamin D is needed early by all babies, whether breast or artificially fed. Vitamin C is needed early by artificially fed babies and is a harmless safeguard for the breast fed baby. Babies born prematurely have a need for vitamin C somewhat greater than that of babies born at term, and this need exists from the time of birth. No need for vitamin A from special sources exists. If current custom is in error, it errs in the direction of giving too much vitamin D and too little vitamin C and in not giving either of these early enough

Wood[2] have discussed developments in the human field during the last ten years, Burke[3] has emphasized the major developments especially in human research, and Warkany[4] has summarized the manifestations of pre natal nutritional deficiency demonstrated by animal experimentation

RECENT HUMAN STUDIES INDICATING THAT NUTRI TION IS AN IMPORTANT FACTOR *IN PREGNANCY*

A number of antepartum studies on relatively large numbers of women which have included careful evalua tions of their diets during pregnancy or have provided supplements to their customary diets, have demon strated a surprisingly strong relationship between the character of the maternal diet on the one hand and the course or outcome of pregnancy and the development of the fetus on the other The earliest report of this type to attract attention was based on a study in Toronto, Canada by Ebbs Tisdall and Scott[5] Three groups of women were studied during the last half of pregnancy The diets of the women in one group were supplemented to an excellent nutritional level, another group of women was taught an excellent diet for pregnancy, while the third group remained on poor diets and so served as controls The incidences of abortions premature births stillbirths and neonatal deaths were significantly higher in the group on a poor diet Not only did the women in the groups with supplemented and good diets have healthier babies, but they themselves proved to be better obstetric risks they suffered fewer complications including less tox emia and they had fewer difficulties during labor delivery and the postpartum period The ability of the mother to nurse her infant also appeared to be influ enced by the quality of her diet during pregnancy[6]

2 Garry R C and Wood H O Dietary Requirements in Human Pregnancy and Lactation A Review of Recent Work Nutrition Abstr & Rev **15**: 591 621 (April) 1946
3 Burk B S Nutrition During Pregnancy A Review J Am Dietet A **20** 735 741 (Dec.) 1944
4 Warkany J Manifestations of Prenatal Nutritional Deficiency in Harris R S and Thimann K. V Vitamins and Hormones Advances in Research and Applications New York Academic Press, Inc. 1945 vol 3 pp 73 103
5 Ebbs J H Tisdall F F and Scott W A The Influence of Prenatal Diet on the Mother and Child J Nutrition **22** 515 526 (Nov) 1941 Milbank Mem Fund Quart **20** 35-46 (Jan.) 1942
6 Ebbs J H and Kelly H The Relation of Maternal Diet to Breast Feeding Arch Dis Childhood **17** 212 216 (Dec) 1942

A committee of the People's League of Health of England investigated the influence of nutrition of expectant and nursing mothers on maternal and infant morbidity and mortality Supplementary minerals and vitamins were given to 50 per cent of about 5 000 English women, the remainder serving as controls The reports of this committee[7] indicate that the incidence of toxemia was 30 per cent lower in the group on a supplemented diet than in the control group The committee claimed that a diagnosis of toxaemia cannot be based upon hypertension by itself as this frequently connotes an essential hypertension ' and that the diagnosis of toxemia on the basis of albuminuria, edema, etc, with or without hypertension but generally with hypertension has the advantage of segregating for special study those cases in which the diagnosis of toxaemia rests on a reasonably secure foundation " On this basis the primiparas who received the supplements were found to be protected against toxemia to a significant degree but the results were favorable in the multiparas to a lesser degree The incidence of prematurity on the basis of weeks of pregnancy was decidedly reduced in the supplemented diet group The committee emphasized the importance of this finding since in England about 50 per cent of the infant deaths under 1 month of age are due to prematurity

Another study carried out by the National Birthday Trust Fund and reported by Balfour[8] included nearly 20 000 women chosen from the lowest income groups in England and Wales One group of women was fed a yeast supplement while another group was furnished supplements of vitamins A and D as well as calcium phosphorus and iron All the groups received additional milk so that the chief dietary differences between the groups were in the concentrates fed Differences in age parity and social and economic conditions were in favor of the control group Hence it can be fairly assumed that any favorable results in the experimental group were due to improvements in diet Statistically significant reductions in the stillbirth and neonatal mortality rates were observed particularly in

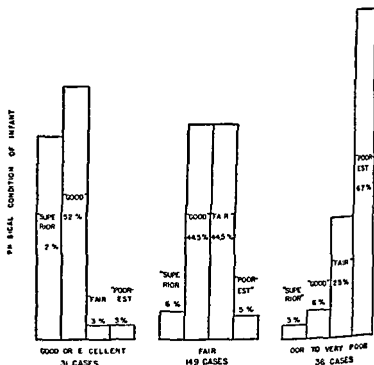
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[7] Nutrition of Expectant and Nursing Mothers Interim Report of the People s League of Health Lancet 2 10-12 (July 4) 1942 The Nutrition of Expectant and Nursing Mothers in Relation to Maternal and Infant Mortality and Morbidity, The People s League of Health J Obst & Gynaec Brit Emp 53 498 509 (Dec) 1946

[8] Balfour M I Supplementary Feeding in Pregnancy Lancet 1 208-211 (Feb 12) 1944

the group fed the vitamin B supplement The maternal deaths were extremely few despite the large number of cases There was a slight but not significant reduction in the incidence of toxemia in the supplemented diet groups

Burke, Beal, Kirkwood and Stuart [9] studied a group of women drawn from the prenatal clinics of the Boston Lying-in Hospital Detailed nutrition histories were obtained at intervals during pregnancy An over all relationship was found to exist between a good or



Relationship of prenatal nutrition to the physical condition of the infant at birth and within first two weeks of life (from Burke, Beal Kirkwood and Stuart [9b])

excellent diet during pregnancy and good physical condition of the infant at birth This relationship is shown in the chart

9 (a) Burke B S Beal V A Kirkwood, S B and Stuart, H. C Nutrition Studies During Pregnancy I Problem Methods of Study and Group Studied II Relation of Prenatal Nutrition to Condition of Infant at Birth and During First Two Weeks of Life III Relation of Prenatal Nutrition to Pregnancy Labor, Delivery and the Postpartum Period *Am. J Obst & Gynec.* **46** 38 52 (*July*) *1943* (*b*) The Influence of Nutrition During Pregnancy upon the Condition of the Infant at Birth J Nutrition **26** 569 583 (Dec) 1943 (c) Burke B S Harding V V and Stuart H C Nutrition Studies During Pregnancy IV Relation of Protein Content of Mother's Diet During Pregnancy to Birth Length Birth Weight and Condition of Infant at Birth J Pediat **23**: 506-515 (Nov) 1943

In the 216 cases studied, all the stillborn infants, all except 1 of the infants who died in the neonatal period, all except 1 of the premature infants, most of the infants with major congenital defects and all the infants con sidered to be functionally immature were born to women in the poorest diet group In contrast, 94 per cent of the infants born to mothers on good or excellent diets during pregnancy were in good or excellent physical condition at birth A significant relationship was found to exist between the antepartun diet and the course of pregnancy although this relationship was less pronounced than that with the condition of the infant at birth The relationship between the general dietary rating during pregnancy and the incidence of toxemia was also significant No statistically significant relationship for primiparous women was found between the antepartum diet and the length of labor However there were many more difficult types of delivery in the poorest diet group despite the fact that these infants at birth averaged almost 3 pounds (1 363 Gm) lighter in weight and several centimeters shorter in length than the infants of mothers whose diets were good or excellent.

Cameron and Graham,[10] working at the Glasgow Royal Maternity and Women s Hospital studied the food intakes of mothers of stillborn infants mothers of prematurely born infants and an equal number of mothers of normal full term infants The average dietary intakes of the mothers with full term infants were superior in all respects the superiority was greatest in protein calcium and phosphorus Apparently the vitamin content of these diets was not evaluated These workers tested the validity of their observations in a practical way *Several hundred women attending the prenatal* clinics of the hospital had their diets carefully supervised during the late months of pregnancy and an equal number whose diets were unsupervised served as controls The average age and parity of the two groups were not significantly different. The incidences of stillbirths and premature births were significantly higher in the groups with unsupervised diets Although there were more neonatal deaths in the control group the difference in this respect was not significant.

10 Cam ron C. S. and Graham, S Antenatal Diet and Its Influence on Stillbirths and Prematurity Glasgow M. J 24 1 7 (July) 1944

Under the severe restrictions imposed by war, England appears to have profited considerably with respect to health as a result of her need to utilize all available food as efficiently as possible Although the diet has been extremely monotonous, the average nutri tional quality of the English diet has improved This has been especially true for the poorer classes to whom are born the major proportion of the infan population Previous to the war the diet of the pregnant woman in the lower income brackets in England[11] was poorer than that of the average adult, but during the war special attention was focused on her diet For the first time in the history of England special food was made avail able to all pregnant women in the form of additional milk, eggs supplementary vitamins and other extra rations when possible The Ministry of Health and the Ministry of Food instituted widespread propaganda programs for the use of these extra rations A study of the stillbirth rates in England and Wales[12] from 1928 through 1944 showed that a sharp drop occurred in all counties after this rationing program was insti tuted In the poorest economic districts the drop has been highest, in Wales for example, it amounted to approximately 35 per cent The neonatal death rate has apparently declined similarly but to a less degree These changes occurred at a time when all conditions of life other than nutrition had deteriorated

Baird[13] in Scotland has shown that among the women in the lower socioeconomic groups the incidence of prematurity was twice the stillbirth rate three times and the neonatal mortality rate four times the com parable rates found in the women of the upper economic groups Baird discussed the fact that the stillbirth and neonatal death rates appear to be controlled by social conditions which operate through the mother He emphasized the fact that in England, Wales and Scot land the stillbirth rate has fallen during the war period and that all age groups and parities have been affected uniformly He referred to the apparent operation of

11 McC nce R A Widdowson E M and Verdon Roe C M A Study of English D ets by the *Indiv dual Method III P egnant Women* at Diff rent Economic Levels J Hyg **38** 596 6 2 (S pt) 1938
12 Suthe land I The St llb rth R te n England and Wales in Rela tion to *Social Influ nc s Lancet* **2** *953 956 (Dec 28) 1946*
13 Baird D The Infl enc of Social and Econom c Facto s on Still births and Neonatal Death J Obst & Gynaec. Brit Emp **52**: 217 234 (June) *339 366 (Aug) 1945*

some factor on a national scale and he considered it probable that improvement in the diets of the poorer women is the explanation.

Severe famine conditions due to war such as those which existed in Holland for a number of months during the winter of 1944 and spring of 1945 and in Leningrad during the siege of that city have contributed also to knowledge of the effect of impaired nutrition during pregnancy on mother and fetus Smith [14] working in Holland found that about 50 per cent of the women suffered from amenorrhea and were presumably infertile during the hunger months and that this disappeared promptly with the return of food The birth rate fell sufficiently to reduce the number of births nine months later to about one third of the usual number The birth weights of infants born at full term decreased abruptly during the hunger months and rose almost as abruptly as Holland emerged from this severe starvation period A significant decline in birth length was also noted but was less pronounced than the change in weight Other effects presented by Smith were given with caution as to their statistical reliability because of Holland s abnormal conditions The available data in regard to abortions were considered useless There appeared to be only a slight increase in premature births while the frequency of stillbirths and neonatal deaths in hospitals was not increased A slight but not significant increase in congenital malformations did occur The sharp fall in the conception rate associated with amenorrhea may have so altered the situation as Antonov [15] suggested as to have allowed only those women to become pregnant whose nutritional state was better than most or who for one reason or another received additional food As a result of studies carried out in Leningrad Antonov found that in the first half of the period of the siege the stillbirth rate rose to 5 6 per cent or twice the normal figure the rate of premature births rose to the unusually high figure of 41.2 per cent and the neonatal death rate to 21 2 per cent The total number of births in this period in the Leningrad

14 Smith C A Effects of Maternal Undernutrition upon the New born Infant in Holland (1944 1945) J Pediat. 30 [illegible]9 243 (March) 1947

15 Antonov A N Children Born During the Siege of Leningrad in 1942 J Pediat. 30 250-259 (March) 1947

State Pediatric Institute was 414 Within the next six month period the prevalence of amenorrhea was widespread, and, owing to a further sharp drop in the birth rate in Leningrad, only 79 women entered the institute for delivery Among these the rates for prematurity, stillbirths and neonatal deaths were within normal lim its It was shown that for various reasons the majority of these women had considerably better food than was usual at that time

Toverud[16] reported a study of approximately 1 000 pregnant women in a special health district of Oslo who as a part of prenatal care, were given nutritional guidance during pregnancy Her results indicate clearly a relationship between the maternal diet the mother's health and course of pregnancy, as well as benefits to the newborn infant The stillbirth rate in the supervised group for the years 1939 to 1944 averaged 16 per thousand live births compared to 30 per thousand for the city of Oslo, and the neonatal death rate was 11 per thousand compared to 20

RESULTS OF MATERNAL DIETARY DEFICIENCY DURING PREGNANCY IN EXPERIMENTAL ANIMALS

In the literature dealing with animal experimentation there are many illustrations of fetal damage resulting from maternal dietary deficiency The recent work of Warkany[17] and his associates in relation to congenital malformations is extremely important He stated that

> Genetics infectious and actinic factors have been proved to be etiologic principles leading to malformations in mammals including man It has been suspected many times that malnutrition of the embryo can also be an etiologic factor

Warkany has shown that in the maternal diet of the rat the presence or absence of sufficient riboflavin between the thirteenth and the fifteenth day of gestation is a decisive factor in the normal development of the skeleton of the embryo Riboflavin is known to be essential for normal growth in that it is essential to cell respiration and it would appear to be necessary also for normal embryonic differentiation When the maternal diet of the experimental animal is made defi

16 Toverud K U Beretn ng om de Første 6 ars arbe d vei Oslo kommunes helse tasjon for mor og barn pa Sagene (1939 1944) Oslo Fabritius and Sønner 1945 pp 1 158

17 Warkany J Congenital Malformations Induced by Maternal Nutritional Deficiency J Pediat. 25 : 476 480 (Dec) 1944

cient in vitamin D, Warkany[18] has shown that mal formations of an entirely different type result More recently these same workers have demonstrated the development of certain congenital defects of the eye together with certain tissue defects in rats when the maternal diet is deficient in vitamin A[19]

Warkany[20] offered the following explanation of the maternal fetal relation in which congenital malformations may result

> The stores of the maternal tissues act as buffers" which prevent deprivation of the developing embryo as long as possible In fact, it was assumed until recently that these maternal stores either protect the offspring completely thus resulting in the delivery of normal young or that in the case of extreme dietary deficiency the embryos die in utero Although there is some truth in this all or none theory it is not entirely correct. Between these two there exists a narrow range in which maternal nutritional deficiency may result in arrest of the embryos development without causing death In this case congenitally deformed offspring may be the result.

No one thus far has proved a relation between congenital malformations in man and maternal nutritional deficiency

RECOMMENDED NUTRITIONAL ALLOWANCES FOR PREGNANCY

With such strong evidence that good diet during pregnancy lessens the likelihood of complications and contributes to a safer labor and delivery there would seem to be ample reason for intensive efforts on the part of obstetricians and general practitioners to improve the diets of all pregnant women coming to them for prenatal care The added evidence that women who have excellent or good diets during pregnancy are much more likely to have healthy well developed infants and much less likely to have stillborn or prematurely born infants or infants who die in the neonatal period, increases the incentive to improve maternal dietaries

The nutritional allowances for pregnancy (fourth through ninth months) as recommended by the Food

18 Warkany J Effect of Maternal Rachitogenic Diet on Skeletal Development of Young Rat, Am J Dis Child. 66 511 516 (Nov) 1943

19 Warkany J and Schraffenberger E. Congenital Malformations Induced in Rats by Maternal Vitamin A Deficiency I Defects of the Eye Arch Ophth 35:150 169 (Feb) 1946

20 Warkany J and Schraffenberger E. Congenital Malformations Induced in Rats by Maternal Nutritional Deficiency VI The Preventive Factor J Nutrition 27:477-484 (June) 1944

and Nutrition Board of the National Research Council[21] are given in table 1, as well as the daily allowances recommended for the normal woman (sedentary) and for the lactating woman

While many persons consider these allowances to be liberal, it should be remembered that they were designed to serve as guides and that they include a margin of safety over the minimum requirement for each nutrient (i e, the amount which will just prevent clinical signs and symptoms of deficiency) In advising women in regard to their diets during pregnancy, our aim should

Recommended Daily Nutritional Allowances Normal Woman Pregnancy and Lactation

(Food and Nutrition Board National Research Council[21])

Nutritional Essentials	Normal	Pregnancy (4th Through 9th Month)	Lactation
Calories	2 000	2 400	3 000
Protein (Gm)	60	85	100
Calcium (Gm)	1 0	1 5	2 0
Iron (mg)	12	15	15
Vitamin A I U †	5 000	6 000	8 000
Ascorbic acid (mg)	70	100	150
Thiamine (mg)	1 0	1 5	1 5
Riboflavin (mg)	1 5	2 5	3 0
Niacin (mg)	10	15	15
Vitamin D I U		400	400

Energy requirements vary with activity size of the person etc.
† The requirement for vitamin A may be less if it is provided as vitamin A and may be more if chiefly in the form of carotene

be to assure that enough of each nutrient is included in the food actually eaten to provide for the best possible health during pregnancy and in preparation for labor delivery and the postpartum period as well as to provide an environment which will permit the optimum growth and development of the fetus These allowances presuppose that women enter pregnancy in optimum nutritional condition a supposition which is often far from true Although the increased requirements up to the fourth month are so small as to be negligible, if the diet has not been good previous to pregnancy

21 Recommended Dietary Allowances Food and Nutrition Board, National Research Council Reprint and Circular Series no. 129 revised 1948 p 31

it should be improved as soon as pregnancy is recognized Ideally, women should be taught as a part of their general education that it is important to enter pregnancy in excellent nutritional state If Warkany's findings in relation to congenital malformations in animals are even in part applicable to man, correcting the diet of the pregnant woman after the first three months would not be effective in preventing congenital malformations if deficient diet is a factor It is probably true that a woman's long time food habits prior to pregnancy her diet early in pregnancy and her diet during the latter part of pregnancy all have important, although possibly different effects on both the mother and fetus To change a woman's food habits to any extent is a difficult task, she must be motivated to do so and the woman who is found to have poor food habits in pregnancy has probably had the same habits for a long time in fact her food habits often represent long time family dietary patterns

CALORIES AND WEIGHT GAIN DURING PREGNANCY

The energy requirement is given by the National Research Council as 2 400 calories, an increase of approximately 20 per cent above the normal requirement under sedentary conditions However, the caloric requirement varies widely with activity The important consideration is that the diet during pregnancy is a much more special diet than is often appreciated because as pregnancy advances the requirements for protein minerals and vitamins are increased in some instances approximately 100 per cent (table 1), while at no time is the caloric requirement more than about 20 per cent above the woman s normal energy needs Because it takes approximately 2 000 calories of carefully selected food to carry these structural and regulatory requirements the freedom of choice is narrowed considerably during pregnancy in comparison to the normal diet in which only about 1 200 calories are needed to carry the protein minerals and vitamins

The increased energy requirement during pregnancy is due to increased basal metabolic rate from the fourth month to term According to Root and Root [22] the

22 Root, H F and Root, H K The Basal Metabol m During Pregnancy and the Puerpe ium Arch. Int. Med. 32:411 424 (Sept) 1923

and Nutrition Board of the National Research Council [1] are given in table 1, as well as the daily allowances recommended for the normal woman (sedentary) and for the lactating woman

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21 Recommended D etary Allowances Food and Nut t on Board Nat onal R sea ch Council Reprint and Circular S es no 129 rev sed 1948 p 31

again is evidence that the fetus is parasitic on the mother to a degree, depending on the mother's nutritional condition when she enters pregnancy as well as on the quality and quantity of her diet during pregnancy

PROTEIN

The protein allowance recommended by the Food and Nutrition Board of the National Research Council for *the latter half of pregnancy is 85 Gm daily or approximately* 1 5 Gm per kilogram of body weight This represents an increase of 40 to 50 per cent above normal Whatever the exact requirement may be, there is no doubt that the amount of protein needed for pregnancy is increased considerably over the normal Nitrogen balance studies by several workers [28] have shown that women store normally relatively large amounts of protein during pregnancy over and above that needed by the fetus and the accessory structures These metabolism studies indicate that a protein requirement of 845 to 900 Gm (135 to 145 Gm of nitrogen) above maintenance is representative of the total net requirement for the fetus and its adnexa during gestation and that under favorable circumstances a woman retains an additional storage of 1,250 to 2 500 Gm of protein (200 to 400 Gm of nitrogen) These figures represent an increased requirement of 10 to 20 Gm of protein daily during the latter months of pregnancy

A negative nitrogen balance sets in abruptly just before term [29] and there is a substantial loss of nitrogen from the maternal organism during parturition and the postpartum period *For women who nurse their infants* there is an additional loss in the breast milk amounting to 1 to 1 5 Gm of nitrogen daily depending on the amount of milk secreted Thus it is usual to find a negative nitrogen balance throughout the puerperium

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28 (*a*) Hunscher H A Donelson, E Nims B Kenyon, F, and Macy I G Metabolism of Women During the Reproductive Cycle V Nitrogen Utilization J Biol Chem. **99**: 507 520 (Jan) 1933 (*b*) Coons C M Schiefelbusch A T Marshall, G B and Coons R. R. Studies in Metabolism During Pregnancy Bulletin 223 Oklahoma Agricultural and Mechanical College Agricultural Experiment Station March 1935, pp 1 113 (*c*) Adair F L Deckmann W J Michel H Dunkle F Kramer S and Lorang E Calcium, *Phosphorus Iron and* Nitrogen Balances in Pregnant Women Am J Obst. & Gynec. **46**: 116-121 (July) 1943 (*d*) Oberst F W, and Plass E D Calcium Phosphorus and Nitrogen Metabolism in Women During the Second Half of Pregnancy and in Early Lactation ibid. **40** 399-413 (Sept.) 1940

29 Macy I G and Hunscher, H A. Evaluation of Maternal Nitrogen and Mineral Needs During Embryonic and Infant Development, Am. J Obst. & Gynec. **27**: 878 888 (June) 1934

basal metabolic rate is elevated 23 per cent at term The increase has been shown by Carpenter and Murlin [23] to be due largely to fetal tissue, which has a higher specific metabolism per unit of weight than maternal tissue They found that the basal metabolic rate of the woman just before delivery was equal to the rates of the mother and infant taken separately a few days after delivery More recent work by Rowe and Boyd [24] and Johnston Hunscher, Macy and others [25] indicates that it is elevated about 15 to 20 per cent above normal and that its elevation may also be subject to hormonal changes occurring in pregnancy Sontag, Reynolds and Torbet [26] claimed that some women have an increase in basal rate of 30 per cent or more during gestation while others show an actual decline in rate

The pregnant woman should be allowed to gain 20 to 25 pounds (9 1 to 11 4 Kg) above her ideal normal weight for height age and build This implies that the underweight woman should be allowed to gain more and the overweight woman should be carefully controlled by restricting calories only while the structural requirements are fully met Kerr [27] reported an average gain of 22 9 pounds (10 4 Kg) in a case study of 500 normal primiparas He found that increasing weight gains in pregnancy are associated with increasing weights of infants at birth but that the latter increase has no influence on the duration of labor Unpublished data by Burke indicate that if an underweight woman gains as much as or more during pregnancy than a normal or overweight woman, she tends to give birth to a smaller infant her own body showing a net gain at the expense of her fetus Conversely if an overweight woman restricts her calories sufficiently she experiences a net loss in weight herself but her infant tends to be heavier than average Here

23 Carpenter T M and Murlin J R The Energy Metabolism of Mother and Child Just Before and Just After Birth Arch Int Med. 7: 184 222 (Feb) 1911
24 Rowe A W and Boyd W C The Metabolism in Pregnancy IX The Foetal Influence on the Basal Rate, J Nutrition 5 551 569 (Nov) 1932
25 Johnston J A Hunscher H A Hummel F Bates, M F Bonner P and Macy I G The Basal Metabolism in Pregnancy J Nutrition 15: 513 524 (May) 1938
26 Sontag L W Reynolds E L and Torbet V The Relation of Basal Metabolic Gain During Pregnancy to Nonpregnant Basal Metabolism Am J Obst & Gynec 48: 315 320 (Sept.) 1944
27 Kerr A Jr Weight Gain in Pregnancy and Its Relation to Weight of Infants and to Length of Labor Am. J Obst & Gynec 45: 950 960 (June) 1943

even for their normal needs and do not change their habits appreciably during pregnancy Careful instruction in regard to the protein foods needed during pregnancy is therefore essential The pregnant woman needs to be taught the importance of 1 quart of milk (about 1 000 cc.) daily (for its 32 Gm of protein), at least ¼ pound (113 Gm) of lean meat or its equivalent (for its 24 Gm of protein) and an egg or equivalent daily (for another 6 Gm) These animal foods or their equivalents will furnish approximately 65 Gm of protein of high biologic value A potato together with at least four servings of bread and cereal foods and the other necessary foods in a well balanced diet will furnish about 20 to 25 Gm more protein in the day's diet

Amenorrhea noted by Smith in Holland and *Antonov* in Leningrad as a result of recent war conditions and already mentioned also has been described by Sydenham[33] *among British civilians in Stanley Camp Hong* Kong, China Sydenham concluded that although emotional shock or change of environment may have *explained many of the irregularities of menstruation* and cases of amenorrhea of short duration the 53 7 per cent of women with amenorrhea lasting more than *three months—in some cases lasting a year or more*—could hardly be explained on this basis He stated that malnutrition especially deficiency of protein appeared to be the most probable cause

The role of protein in relation to toxemia of pregnancy is still a debated problem Arnell[31] found a higher incidence of toxemia among patients with a low protein diet than among those with a liberal intake Holmes[34] reported the incidence in women taking low protein diets to be twice as great as that in similar groups taking high protein diets Burke and others[26] found a significant relationship between the incidence of preeclampsia and the general antepartum dietary rating While the protein intake was low in many of these cases many other dietary essentials were *also low so that it was not possible* to conclude that protein was the sole dietary factor involved We wish to emphasize the difficulty in human studies of proving

33 Sydenham A Amenorrhoea at Stanley Camp Hong Kong During Internment, Brit M J 2 159 (Aug 3) 1946
34 Holmes O M Protein Diet in Pregnancy West. J Surg 49 56 60 (Jan) 1941

and often during the lactation period as well The storage of nitrogen during pregnancy may, therefore be regarded in part as a natural mechanism to provide in advance for the large losses occurring during delivery and the puerperium and in part as preparation for the high requirements of lactation

In addition to the nitrogen balance studies already discussed the recent studies of Burke and others[9c] indicate that less than 75 Gm of protein daily during the latter part of pregnancy results in an infant who tends to be short, light in weight and likely to receive a low pediatric rating in other respects

If it is assumed that an allowance of 60 Gm (approximately 1 Gm per kilogram of body weight) is desirable for the average nonpregnant woman and that an increase of 15 to 20 Gm daily is needed in the latter part of pregnancy, the protein allowance of 85 Gm daily suggested by the Food and Nutrition Board of the National Research Council appears liberal and adequate to care for individual differences Williams[30] emphasized the important point that this figure presupposes a previously normal protein intake and nutritional state

The question arises how nearly the diets of pregnant women approximate this allowance Burke and others[9c] in studies at the Boston Lying-in Hospital found that only 10 per cent of the women were consuming 85 Gm of protein daily while 68 per cent consumed less than 70 Gm, 38 per cent less than 55 Gm and 14 per cent less than 45 Gm of protein daily during this important period of fetal growth and development Arnell and others[31] found that among pregnant women in New Orleans 18 per cent took less than 42 5 Gm of protein daily i e less than half the recommended allowance, and 79 per cent took less than 70 Gm daily Williams and Fralin[32] in Philadelphia showed that only 13 per cent were taking the recommended daily allowance It should be emphasized that an amazingly large number of women do not eat a diet well supplied with protein

30 Williams P F Importance of Adequate Nutrition in Pregnancy J A M A **127** 1052-1055 (April 21) 1945

31 Arnell R E Goldman D W and Bertucci F J Protein Deficiencies in Pregnancy J A M A **127** 1101 1107 (April 28) 1945

32 Williams P F and Fralin F G Nutrition Study in Pregnancy Dietary Analyses of Seven Day Food Intake Records of Five Hundred Fourteen Pregnant Women Comparison of Actual Food Intakes with Variously Stated *Requirements* and *Relationship of Food Intake to Various* Obstetric Factors, Am J Obst. & Gynec. **43** 1 20 (Jan) 1942

studies indicate that 1 5 Gm of calcium daily during the latter half of pregnancy should allow sufficient calcium to meet the needs of the fetus and also permit an additional storage of calcium in the mother in preparation for lactation Swanson and Iob[39] have shown that 65 per cent of the calcium and 64 per cent of the phosphorus of a full term fetus are deposited in the last two months of pregnancy

The phosphorus requirement is somewhat higher than the calcium requirement and is probably in the neighborhood of 2 Gm in the latter part of pregnancy There need be little concern about phosphorus however, since the protein rich foods are liberally supplied with it and when protein and calcium needs are cared for phosphorus will usually be supplied in ample amounts

Since vitamin D appears to aid in the utilization and retention of these two minerals some additional source of this vitamin a total of 400 international units has been recommended daily Liu and co-workers[40] and others have found that in the presence of an adequate supply of vitamin D the same degree of calcium retention is maintained on a somewhat lower intake of calcium but that in severe vitamin D depletion high levels of calcium and phosphorus will not maintain the subject in balance The calcium and phosphorus requirements may well be conditioned by such factors as previous calcium and phosphorus stores dietary custom and state of vitamin D nutrition The protein and calcium requirements are also related[41]

From a practical standpoint it should be remembered that the majority of women today enter pregnancy with low calcium stores and with poor food habits in regard to calcium rich foods namely milk and its products One quart of milk furnishes 1.2 Gm. of calcium, and only approximately 0 3 Gm can be obtained from other foods in the usual diet Without this amount of milk therefore it is impossible to meet fully the recommended calcium allowance of pregnancy

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39 Swanson W W and Iob L. V The Growth of Fetus and Infant as *Related to Mineral Intake During Pregnancy* Am. J Obst. & Gynec. **38** 382 391 (Sept) 1939

40 Liu S H Chu, H I Hsu, H. C. Chao, H C and Cheu, S H Calcium and Phosphorus Metabolism in Osteomalacia XI The Pathogen c Role of Pregnancy and Relative Importance of Cal ium and V tamin D Supply J Clin. Investigation **20** 255-271 (May) 1941

41 McCance, R. A Widdowson E. M. and Lehmann H Effect of Pr t n Intak on Absorption of Calcium and Magnesium, Biochem. J **36**: 686-691 (Sept.) 1942.

conclusively that a given nutrient is responsible for a given effect Strauss[35] has contended that in the presence of protein insufficiency the colloid osmotic pressure of serum protein is altered This causes edema and a consequent disturbance of the electrolyte balance which, in turn, may result in elevation of the blood pressure and other symptoms of toxemia

Dieckmann[36] has, however, expressed the view that toxemia and a low protein intake are not related More over, reports from certain areas in which starvation occurred in World War II have indicated that the inci dence of toxemia fell sharply among pregnant women during the period of extreme food restriction Smith[37] gave figures regarding the incidence of toxemia in Holland showing that during the months of acute hunger the incidence fell sharply He discussed the possible explanations of this sharp contrast in findings

Although there is still controversy among well informed persons concerning the cause of toxemia, it is generally accepted that a high protein diet does not predispose to the condition The major weight of evi dence would seem to indicate that toxemia occurs more often among chronically malnourished women than among well nourished women and that protein is one of the factors frequently deficient The subject would appear to be an important one for further investigation

For a further discussion of the effects of protein deficiency on both mother and fetus the reader is referred to a paper on the subject by one of us[38]

CALCIUM PHOSPHORUS AND VITAMIN D

As a result of balance studies of Macy,[29] Coons[28b] and more recently Dieckmann,[28c] Oberst and Plass[28d] and others, it is an accepted fact that calcium and phos phorus requirements are considerably increased during pregnancy, if the maternal organism's own stores are to be maintained and fetal needs met While the exact requirement for calcium is not known these balance

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35 Strauss M B Observations on Etiology of Toxemias of Preg nancy IV Primary Role of Plasma Proteins in Conditioning Water Retention and Edema Formation in Normal and Toxemic Pregnancy Am J M Sc **195**:7 37 8 (June) 1938

36 Dieckmann W J Edema in Pre Eclampsia and Eclampsia, Am J Obst & Gynec **41**:1 16 (Jan) 1941

37 Smith C A The Effect of Wartime Starvation in Holland upon Pregnancy and Its Product Am J Obst & Gynec **53**:599 608 (April) 1947

38 Stuart, H C Effects of Protein Deficiency on the Pregnant Woman and Fetus and on the Infant and Child New England J Med **236**:507 513 (April 3) 537 541 (April 10) 1947

great variations in the calcification of the teeth He stated that this calcification is determined not only by the age of the fetus but also by the nutritional and general physical condition of the mother Mellanby and Coumoulos,[47] Toverud and Toverud[48] Burke[49] Berk[50] and Massler and others[51] have accumulated data which indicate that the structure of the deciduous teeth is related to the prenatal diet It would appear that unless the maternal diet allows for a liberal storage of calcium and other substances essential to sound tooth structure in the infant's body at birth, tooth structure may be further impaired in the early months of infancy

IRON

The iron allowance of 15 mg recommended for the latter months of pregnancy assumes that the woman enters pregnancy with adequate stores of iron and a normal hemoglobin level Many women have depleted iron stores and a low hemoglobin level at this time While balance studies by Coons[52] and Toverud[53] indicate that 15 mg of iron are sufficient in many cases Macy and Hunscher[9] considered 20 mg a safer allowance In a recent publication Toverud[16] favored 20 mg of iron during the latter part of pregnancy to assure a positive balance Various workers have shown that anemia during pregnancy is common both in this country and elsewhere and it is generally accepted that the hemoglobin level is affected by diet Garry and Wood[2] rightfully deplored the lack of detailed information concerning the normal behavior of blood volume

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47 Mellanby M and Coumoulos H The Improved Dentition of Five Year Old London School Children A Comparison Between 1943 and 1929 *Brit M J* 1 837 840 (June 24) 1944

48 Toverud K U and Toverud G Studies on the Mineral Metabolism During Pregnancy and Lactation and Its Special Bearing on the Disposition to Rickets and Dental Caries *Acta Pædiat.* (supp 2) **12** 1 116 1931

49 Burke, B S Study of the Nutrition of Groups of Children *Selected on the Basis of No Defective Deciduous Teeth and High Incidence* of Defective Deciduous Teeth Child Development **11** 327 334 (Dec.) 1940

50 Berk H Some Factors Concerned with the Incidence of Dental Caries in Children Multiple Pregnancy and Nutrition During Prenatal Postnatal and Childhood Periods J Am. Dent. A. **30**: 1749 1754 (Nov) 1943

51 Massler M Schour I and Poncher H G Developmental Pattern of the Child as Reflected in the Calcification Pattern of the Teeth, Am J Dis. Child **62** 33 67 (July) 1941

52 Coons, C M Iron Retention by Women During Pregnancy J Biol. Chem **97** 215-226 (July) 193_

53 Toverud, K. U *Investigation on the Ironstore of Newborn Infants*, Acta Pædiat. (supp. 1) **17**: 136-140 1935

Milk must also be depended on for much of the phosphorus needed Calcium tablets should not be recommended as a milk substitute for the pregnant woman because considerable dependence also must be placed on milk as a source of other required nutrients It has already been emphasized that the pregnant woman's need for protein is high and that 1 quart of milk daily supplies a little more than one third of that protein Whole milk also is an important source of riboflavin thiamine and vitamin A In addition the number of calcium pills required to furnish the calcium equivalent of 1 quart of milk is so large that it usually will not be taken and will if taken often cause constipation

Maxwell[42] has reported in considerable detail a number of cases of congenital rickets in the newborn of Chinese women suffering from osteomalacia Dunham[43] and Rector[44] have also shown that fetal rickets or rickets in the early weeks of life may result from lack of calcium, phosphorus or vitamin D in the prenatal period

Prenatal studies carried out by our associates and us[45] have shown a relationship between both the protein and the calcium content of the antepartum diet and the osseous development of the infant at birth This was indicated by the presence or absence of certain osseous centers in roentgenograms of the hand, knee and foot While both relationships are strong, that with protein appears to be somewhat stronger than that with calcium A similar relationship has also been shown by these workers between the amount of calcium in the tooth buds as seen in lateral roentgenograms of the head at birth and the protein content of the maternal diet A somewhat weaker relationship was also shown with the calcium content of the mother's diet Toverud[46] reported that roentgenograms of newborn infants show

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42 Maxwell J P Further Studies in Adult Rickets (Osteomalacia) and Foetal Rickets Proc Roy Soc Med 28: 65 300 (Jan) 1935

43 Dunham E C Rickets in an Infant of Thirty Four Days Am J Dis Child 26 155 163 (Aug) 1923

44 Rector J M Prenatal Influence in Rickets I Fetal Rickets II Early Postnatal Rickets and Florid Rickets with Multiple Fractures J Pediat 6 161 177 (Feb) 1935

45 Stuart, H C Findings on Examinations of Newborn Infants and Infants During the Neo-Natal Period Which Appear to Have a Relationship to the Diets of Their Mothers During Pregnancy Federation Proc. 4 271 281 (Sept) 1945

46 Toverud, G Preventive Dentistry in the Pre school Period and Particularly During Foetal Life Dent Mag & Oral Topics 55: 299 310 (April) 1938

VITAMINS

Vitamin D has already been discussed in relation to the requirements for calcium and phosphorus Undoubtedly pregnancy increases the need for all the vitamins but our actual knowledge in this field is limited, and much investigation is necessary before the requirements for the various vitamins during pregnancy can be stated with any degree of exactitude Until more definite information is available the Recommended Allowances of the National Research Council seem desirable, although they may be unnecessarily liberal in some instances It is better to err on the side of liberality in these instances since there is no indication that a moderate excess is potentially harmful and considerable harm may result from a deficiency during a period of rapid growth

Vitamin A—The vitamin A requirement of pregnancy is not known and the recommended allowance of 6 000 international units represents an arbitrary increase over normal adult requirements In the average diet about two thirds of the vitamin A value is in the form of carotene a smaller amount would be needed if all were provided as vitamin A This amount is readily supplied in the daily diet by whole milk, eggs butter or fortified oleomargarine and by the inclusion several times each week of a liberal serving of a dark leafy green or deep yellow vegetable Liver at least once a week improves considerably the vitamin A content of the diet Since most of the vitamin A is removed when milk is skimmed it is much better not to substitute skim for whole milk as a means of reducing the caloric value of the diet but rather to remove less desirable foods when necessary to limit calories Mineral oil should not be used as a laxative or in salad dressing or other food combinations, especially during pregnancy since it absorbs both carotene and vitamin A

Byrn and Eastman,[57] Bodansky and associates [58] Lund and Kimble [59] as well as others have shown that

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57 Byrn J N and Eastman N J Vitamin A Levels in Maternal and Fetal Blood Plasma Bull. Johns Hopkins Hosp **73**: 132 137 (Aug) 1943

58 Bodansky O, Lewis J M and Lillienfeld M C. C. The Concentration of Vitamin A in the Blood Plasma During Pregnancy J Clin Investigation **22**: 643 647 (Sept) 1943

59 Lund C J and Kimble, M S Vitamin A During Pregnancy Labor and the Puerperium, Am. J Obst. & Gynec. **46**: 486-501 (Oct.) 1943

of plasma volume and of the volume of packed red cells during pregnancy" Without such standards red cell counts and hemoglobin values are misleading

In India a macrocytic hypochromic anemia is common during pregnancy and is a cause of high infant and maternal mortality Napier and Edwards[54] have reported studies on 529 pregnant women in India Although there was evidence of widespread secondary anemia, the majority of cases of anemia were also macrocytic in type This type of anemia was also thought to be of nutritional origin, because of its higher incidence in the lower economic groups When macrocytic anemia was encountered among the wealthy, a high incidence of vegetarianism resulting in diets of low protein quality and quantity was found Bethell[55] has also reported this type of anemia, although its incidence in this country is not common It has been found to yield usually to an increased intake of protein and/or of the vitamin B complex In India liver therapy is often used Recently folic acid[56] has been used successfully in treating macrocytic anemia of pregnancy

One of the major causes of anemia of early infancy may be insufficient iron stores in utero resulting from anemia of the mother during pregnancy

Iron in the diet comes in relatively small amounts from a number of foods Food sources of iron include lean meat, liver egg potato, fruit (especially dried fruits), vegetables (especially greens and legumes), whole grains or enriched breads and cereals and molasses If the pregnant woman has hypochromic anemia medicinal iron should be given routinely in addition to a well balanced diet

IODINE

In regions where goiter is endemic iodine should receive especial consideration since the physiologic changes incident to pregnancy may result in deficiency symptoms in either mother or infant or both

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54 Napier L. E and Neal Edwards M L Anaemia in Pregnancy in Calcutta An Analysis of Haematological and Other Data from Five Hundred and Twenty Nine Pregnant Women Indian M Research Mem December 1941 no 33 pp 1 135

55 Bethell F H Blecha, E., and Van Sant J G Nutritional Inadequacies in Pregnancy Correlated with the Incidence of Anemia, J Am Diete. A. **19** 165 172 (March) 1943

56 Spies T D Effect of Folic Acid on Persons with Macrocytic Anemia in Relapse, J A. M A **130**: 474-476 (Feb 23) 1946

as much thiamine is required during late pregnancy as under normal conditions Toverud[16] in a recent publication confirmed his observation and suggested that on this basis the optimum thiamine requirement in late pregnancy is about 3 mg

Polyneuritis of pregnancy has been recognized by various workers as due to a deficiency of thiamine McGoogan[64] has reviewed the literature on severe polyneuritis due to vitamin B deficiency in pregnancy He concluded that pernicious vomiting of pregnancy may result in a vitamin B deficiency with a severe polyneuritic syndrome One of us has observed that considerable benefit often is derived when thiamine is given to patients with nausea in early pregnancy and that it is helpful in many cases of pernicious vomiting

Van Gelder and Darby[65] have reviewed the literature on congenital and infantile beriberi They have also reported a case of congenital beriberi in an infant born to a mother who had been on an inadequate diet for several months and who did not herself exhibit any pronounced clinical symptoms of deficiency

The amount of thiamine currently recommended for pregnancy is 1 5 mg daily Dependence must be placed on milk lean meat vegetables especially legumes and potato and whole grain or enriched bread and cereals for the major amount of this vitamin since in the usual diet for pregnancy these foods furnish approximately 80 per cent of the thiamine allowance

Riboflavin —The recommended allowance of this vitamin for the latter part of pregnancy is 2 5 mg daily Adequate amounts of riboflavin are undoubtedly *important in periods of rapid growth and development* Milk furnishes the major portion of riboflavin in the average diet 1 quart supplying approximately 1 6 mg or about 65 per cent of the recommended allowance Liver will furnish 2 5 mg per 4 ounce portion and if used once a week or oftener serves as an additional safeguard to the average intake Dark leafy green vegetables and lean meat are good sources of this vitamin Whole grain or enriched bread and cereal foods other vegetables and eggs contribute most of the remaining riboflavin in the average diet

64 McGoogan L S Severe Polyneuritis Due to Vitamin B Deficiency in Pregnancy Am J Obst & Gynec. 43:75 762 (May) 1942

65 Van Gelder D W and Darby F U Congenital and Infantile Beriberi, J Pediat. 25:2 6-235 (Sept.) 1944

the plasma vitamin A value falls as pregnancy advances Lund and Kimble claimed that the time and amount of the decrease depends in part, at least, on the intake of vitamin A There appears to be an immediate and unfailing postpartum elevation of plasma vitamin A Lund and Kimble[60] also reported that plasma vitamin A values in the newborn infant are independent of the maternal plasma values regardless of the mother's diet ary intake, but that fetal plasma carotene varies regu larly with maternal values Both Byrn and Eastman and Bodansky, Lewis and associates found substantial amounts of vitamin A and some carotene in fetal plasma Bodansky and associates attributed the decrease in plasma vitamin A in the third trimester of pregnancy to storage in fetal liver and to utilization by fetal tissue Lewis, Bodansky and others[61] reported that a supple ment of 10 000 international units of vitamin A or of carotene during the last few months of pregnancy appears to maintain good levels of vitamin A in mater nal plasma but that the vitamin A and carotene levels of the infant's cord blood appear to be no higher than in those infants whose mothers did not receive supple ments

It has already been mentioned that Warkany[19] and *others have shown in animals that certain abnormalities* of the eyes and tissues are due to vitamin A deficiency during pregnancy Maxwell[62] cited a case of kerato-malacia of both eyes at birth in an infant of a Chinese woman who had been on a diet deficient in vitamin A

Vitamin B Complex—The exact requirements for the vitamin B complex during pregnancy are not known but undoubtedly the need is increased, especially in the latter months of pregnancy

Thiamine—Lockhart and others,[63] using the excre tion peak in the urine as an indication of the subject s thiamine status found that approximately three times

60 Lund C J and Kimble M S Plasma Vitamin A and Carotene of the Newborn Infant with Consideration of Fetal Maternal Relationships Am J Obst & Gynec **46**: 207 221 (Aug) 1943

61 Lew s J M Bodansky O Lillienfeld M C C and Schneider H Supplements of Vitamin A and of Ca otene Dur ng Pr gnancy, Their Effect on the Levels of Vitamin A and Carotene in the Blood of Mother and of Newborn Infant Am J Dis Child **73**: 143 150 (Feb) 1947

62 Maxwell J P Vitamin Deficiency in the Antenatal Period Its Effects on the Mother and Infant J Ob t & Gynaec. Br t. Emp **39** 764-776 1932

63 Lockhart, H S Ki kwood S B and Harris R S The *Effect* of Pregnancy and Puerper um on the Th amine Status of Women Am J Ob t. & Gynec **46** 358 365 (Sept.) 1943

respect to the fetal maternal relationship of this vitamin Both groups found that the plasma level in the cord blood of the infant is always higher than that of the maternal blood and when the latter is low the difference between the two becomes proportionately greater Maternal plasma levels of ascorbic acid were found to reflect the current dietary level and it was also found that an increasing intake of ascorbic acid was necessary during the latter part of pregnancy to maintain the same plasma level While none of the published studies include any cases in which the maternal plasma value was zero it seems reasonable to suppose that in such a case the fetus would suffer and that fetal scurvy could result if the condition persisted Fetal scurvy[71] has been reported in the literature.

The recommended allowance of 100 mg of ascorbic acid daily is supplied by 8 ounces (227 Gm) of unstrained orange juice or by proper amounts of other foods rich in this vitamin, such as tomatoes grapefruit, raw cabbage raw or properly cooked leafy green vegetables or potatoes cooked in the skin

Vitamin E (Alpha Tocopherol) —Vitamin E is of interest in its possible relation to habitual abortion This vitamin has never been proved to be essential to man and the possibility of deficiency in the average human diet is considered remote. Shute[72] has discussed this problem thoroughly

Vitamin K—Since vitamin K is present in certain foods and is also synthesized by bacterial action in the intestinal tract the possibility of a deficiency in the mother seems unlikely under normal conditions However the newborn infant has a very low store of vitamin K and hemorrhagic disease of the newborn is associated with this deficiency The administration of vitamin K to the mother in the last weeks of pregnancy or just prior to or during labor increases the prothrombin time of the infant and apparently reduces the incidence of evidences of this deficiency[73] It is

71 L o k B *Case of Infantile Scurvy in the Newborn, China M. J* 45 995 996 (Oct) 1931

72 Shute E Vitamin E in Habitual Abortion and Habitual Miscarriage J Obst & Gynaec. Brit. Emp 49: 534-541 (Oct.) 1942 Vitamin E and Premature Labor Am. J Obst. & Gynec. 44 271 279 (Aug) 194

73 Shettles, L. B Delfs E and Hellman L. M Factors Influencing Plasma *Prothrombin in the Newborn Infant* II Antepartum and Neonatal Ingestion of Vitamin K Concentrates Bull. Johns Hopkins Hosp 65: 419-426 (Nov) 1939 Bruchsaler F S Vitamin K and the Prenatal and Postnatal Prevention of Hemorrhagic Disease in Newborn Infants, J Pediat. 18: 317 330 (March) 1941

Braun and others[66] reported manifestations of riboflavin deficiency in 21 per cent of the cases in a series of 900 Jewish women These women belong to the poorer economic classes in Palestine Glossitis and heartburn were symptoms common to all cases, many of the women also showed symptoms of cheilosis, corneal vascularization and angular stomatitis The symptoms appeared usually in the third trimester of pregnancy, and the amount of riboflavin excreted in the urine was low The average daily intake of these women was under 1 3 mg When they were treated either with riboflavin or yeast extract their symptoms improved

Warkany[20] as has been stated has shown a relationship between riboflavin deficiency in the rat and certain skeletal defects

Niacin—Although 15 mg of niacin are recommended for pregnancy, little is known about the human requirement Lean meat liver legumes potato and whole grain or enriched bread and cereal foods contribute the major portion in the average diet Milk while a poor source of niacin is a good source of tryptophan, which may function as a precursor of niacin[67]

Pyridoxine (Vitamin B_6)—Mention should be made of the use of pyridoxine in the prevention of severe nausea and vomiting of pregnancy[68] While there seems to be some difference of opinion about the success of its use in this respect, the worker preferred to consider it helpful

Ascorbic Acid—The ascorbic acid requirement has been shown to be increased considerably during the latter part of pregnancy The findings of Lund and Kimble[69] substantiate those of Teel and others[70] in

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66 Braun, K Bromberg Y M and Brzezinski A Riboflavin Deficiency in Pregnancy J Obst & Gynaec. Brit Emp **52** 1 12 (Feb) 1945

67 Krehl W A Sarma P S Teply L. J and Elvehjem C A. Factors Affecting the Dietary Niacin and Tryptophane Requirement of the Growing Rat J Nutrition **31** 85 106 (Jan) 1946

68 Weinstein B B, Wohl Z Mitchell G J and Sustendal, G F Oral Administration of Pyridoxine Hydrochloride in the Treatment of Nausea and Vomiting of Pregnancy Am. J Obst & Gynec **47** 389 394 (March) 1944 Hart, B F McConnell, W T and Pickett A. N Vitamin and Endocrine Therapy in Nausea and Vomiting of Pregnancy Am. J Obst. & Gynec **48** 251 253 (Aug) 1944

69 Lund C J and Kimble M S Some Determinants of Maternal and Fetal Plasma Vitamin C Levels Am J Obst. & Gynec **46**: 635 647 (Nov) 1943

70 Teel H M Burke, B S and Draper R Vitamin C in Human Pregnancy and Lactation I Studies During Pregnancy Am. J Dis Child **56** 1004 1010 (Nov) 1938.

energy requirement during lactation may be increased 50 per cent or more above the normal requirement The diet must furnish sufficient calories to meet (1) the mother's own energy requirement (2) the caloric value of the milk secreted (20 calories per ounce [28 3 Gm]) and (3) an additional small caloric requirement used in producing the milk which is estimated to be about 10 per cent of the caloric value of the milk produced

The value of a high protein diet during pregnancy as an important factor in successful lactation has been discussed An even higher protein intake is necessary during the lactation period itself The recommended allowance is 100 Gm daily, or approximately 2 Gm per kilogram of body weight A pronounced deficiency of calories and protein is usually associated with a reduction in the amount of milk produced[77] The calcium and phosphorus requirements are also elevated during lactation the calcium allowance for lactation is about 2 Gm per day and the phosphorus allowance is correspondingly increased Apparently the calcium content of breast milk varies much more widely than is appreciated[78] it probably reflects the calcium content of the maternal diet Balance studies of Macy[9] and others form the bases of these recommendations for protein calcium and phosphorus

The iron requirement during lactation probably is not increased and may be lower than during pregnancy because breast milk is low in iron

The vitamin requirements of the lactation period are not known The recommended allowance for vitamin A has been increased to 8 000 international units daily This increase is explainable by the fact that the vitamin A content of breast milk is high[79] and the infant s stores at birth are apparently relatively low The thiamine allowance of 1 5 mg is the same as that recommended for pregnancy The transfer of thiamine from the mother to breast milk is relatively poor but the maternal diet has been shown to be the principal deter-

77 Garry and Stiven Garry a d Wood.[8] Ebbs and Kelly

78 Stearns G The Mine al Metabol sm of *Normal Infants, Physiol Rev* 19 415 438 (July) 1939

79 Lesh r M Brody J K, W lliams, H H and M cy I G Human Milk St dies XXVI Vitamin A and Ca otenoid Contents of Colostrum and Mature Human Milk, Am J D s Child, 70: 18- 192 (Sept) 1945

still a matter of controversy as to whether or not the administration of vitamin K in this manner has materially reduced the incidence of intracranial hemorrhage at birth [74] However, as Warner stated [75]

> It is logical to assume that the prophylactic administration of vitamin K would decrease the incidence and extent of intracranial hemorrhage at the time of birth in these infants Also the administration of vitamin K might be expected to decrease any danger of late bleeding into the injured areas during the first few postnatal days

FOOD NUCLEUS TO INSURE OPTIMUM NUTRITION DURING PREGNANCY [76]

The following is a summary of the foods or their nutritional equivalents which should be eaten daily

Whole milk	1 quart
Lean meat	At least one liberal serving (4 ounces) liver is desirable at least once each week
Egg	At least one
Fruit	Two or more servings (1 to 1½ cups, 200 to 300 Gm) Two medium oranges, or unstrained orange juice (8 ounces) or its equivalent should be taken each day
Vegetables	Two or more servings of cooked or raw vegetables (1 to 1½ cups, 200 to 300 Gm) these should include dark green leafy or deep yellow vegetables, also legumes several times each week in addition a medium potato (150 Gm.) cooked in the skin should be eaten daily
Bread and cereal	Whole grain or enriched bread at least four slices daily (½ cup cereal is equivalent to 1 slice of bread)
Butter or fortified margarine	2 tablespoons
Additional foods	Consisting of either more of the foods already listed or other foods of one's own choice, adjusted to individual energy needs and in relation to desired weight gain
Vitamin D	Some form of vitamin D to supply 400 international units

NUTRITIONAL REQUIREMENTS AND THE NECESSARY DIETARY ADJUSTMENTS TO INSURE OPTIMUM NUTRITION DURING LACTATION

The nutritional allowances suggested for the lactating woman by the Food and Nutrition Board of the National Research Council are shown in the table The

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74 Parks, J., and Sweet, L. K Does the Antenatal Use of Vitamin K Prevent Hemorrhage in the Newborn Infant? Am. J Obst. & Gynec. 44: 432-442 (Sept.) 194.

75. Warner E. D Vitamin K and Hemorrhagic Disease of the New born in Brennemann, J Practice of Pediatrics, Hagerstown, Md. W F Prior Company Inc. 1936 vol. I ch p 32 A

76 Burke, B S., and Kirkwood S B Daily Diet During Pregnancy Department of Maternal and Child Health Harvard School of Public Health, Boston revised 1946

CHAPTER XVI

NUTRITION PROBLEMS OF GERIATRIC MEDICINE

EDWARD J STIEGLITZ

Human nutrition and metabolism are fundamentally similar throughout the life span The basic needs of the human organism required to maintain health and to permit normal growth and development have been discussed elsewhere in this series But the process of aging produces change and thus the period of senescence or involution presents special problems in nutrition just as does the more dramatic period of conspicuous growth or evolution of infancy and child hood Pediatrics made its greatest advances when it was realized that the child is not merely a little man' but presents nutritional chemical structural functional immunologic and psychologic attributes characteristic of his age or stage of development A similar attitude is essential to comprehensive appreciation of geriatric medicine Older persons are not the same as they were in youth or in the full bloom of physical maturity, they are different in many respects by reason of the changes of aging The effects of aging are most conspicuous at the beginning and the end of the normal life span, though processes of aging are continuous throughout life

Geriatric medicine or the medical care of the aging and the aged [1] is not sharply defined by any arbitrary limits as to the age at which it should begin It is not as yet a formal specialty and it is hoped that it will not become one It is essentially a point of view or attitude of mind which takes cognizance of the physiologic structural psychologic chemical and other changes introduced by aging after the peak of maturity Geri-

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1 Stieglitz, E. J Geriatric Medicine, ed. 2 Philadelphia, W B Saunders Company 1949

minant of the amount so transferred[80] The recommendations of 3 mg of riboflavin and 15 mg of niacin are empiric Macy and others[81] have shown that the concentrations of both of these vitamins are higher in the breast milk of women on diets of high composition than in the milk of women on self-chosen diets The recommended allowance of 150 mg of ascorbic acid rests on a somewhat sounder foundation[82] The ascorbic acid content of human milk is much higher than that of cow's milk[83] The allowance of 400 international units of vitamin D is the same as for pregnancy

Those interested in more detailed information on the nutritional value of breast milk are referred to the recent papers by Macy and her co-workers[84]

To insure an optimum diet throughout lactation each woman should be advised during late pregnancy and in the early postpartum period in regard to the changes which she should make in her diet for the period of nursing An additional pint of milk—i e, a total of 1½ quarts daily—furnishes the additional protein, calcium, phosphorus, riboflavin and thiamine suggested, as well as some of the additional vitamin A and calories Liberal amounts of vegetables and fruits which should include the amount of citrus fruit recommended for pregnancy will cover the ascorbic acid allowance Additional bread, cereals potato and other foods of the woman's own choice usually must be included, because energy requirements are high during this period, but the extent of use of these foods must be varied in accordance with individual needs

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80 Roderuck C E Williams H H and Macy I G Human Milk Studies XXIII Free and Total Thiamine Contents of Colostrum and Mature Human Milk Am. J Dis Child **70** 162 170 (Sept) 1945

81 (*a*) Roderuck C E Coryell M N Williams H H and Macy I G Human Milk Studies XXIV Free and Total Riboflavin Contents of Colostrum and Mature Human Milk Am J Dis Child **70** 171 175 (Sept) 1945 (*b*) Coryell, M N Harris M E. Miller S Williams H H and Macy I G Human Milk Studies XXII Nicotinic Acid Pantothenic Acid and Biotin Contents of Colostrum and Mature Human Milk ibid **70** 150-161 (Sept) 1945

82 Selleg I and King C G The Vitamin C Content of Human Milk and Its Variation with Diet J Nutrition **11**: 599 606 (June) 1936 Ingalls T H Draper R and Teel H M Vitamin C in Human Pregnancy and Lactation II Studies During Lactation Am J Dis Child **56** 1011 1019 (Nov) 1938

83 Lawrence, J M Herrington B L and Maynard L A Human Milk Studies XXVII Comparative Values of Bovine and Human Milks in Infant Feeding Am. J Dis Child **70** 193 199 (Sept.) 1945

84 Lesher Brody Williams and Macy [a] Roderuck Williams and Macy[80] Roderuck and others[14] Coryell and others[81b] Beach E F Bernstein S S Hoffman O D Teague D M and Macy I G Distribution of Nitrogen and Protein Amino Acids in Human and in Cow's Milk J Biol Chem **139** 57-63 (May) 1941 Munks B Robinson A Williams, H H and Macy I G Human Milk Studies XXV Ascorbic Acid and Dehydroascorbic Acid in Colostrum and Mature Human Milk Am. J Dis Child **70**: 176 181 (Sept.) 1945

significant that almost all the so called degenerative diseases have one characteristic in common impairment of the nutrition of parenchymal cells [3]

Nutrition is more than diet Proper nutrition includes not only the ingestion of adequate and balanced quantities of all necessary nutritive elements but also the digestion of foods in the alimentary canal, their absorption, transport to the tissue cells and utilization by the cells Nutrition may be impaired at any one or more points in this chain of activities The internal milieu is the medium through which the integrity of the tissue cells are maintained Fibrotic changes hyalinization of the matrix accumulation of toxic materials in the intercellular fluid and slowed transport are all consequences of the more common degenerative processes Impairment of cellular nutrition may result from any one or more of several factors (1) inadequate nutritional supply (such as dietary deficiencies digestive failure histanoxia of anemia) (2) inefficient distribution (circulatory impairments) (3) ineffective utilization of food elements (hypoinsulinism asphyxia enzyme deficiencies) (4) accumulation of injurious metabolic debris (such as azotemia uric acid deposition)

Malnutrition may thus be endogenous as well as exogenous It includes excesses as well as deficiencies a fact which has been unfortunately ignored by many If normal nutrition is taken as the average or norm of apparently well persons (at least those not grossly or obviously ill) it may differ widely from the optimum As health is relative and never absolute the potentialities of an optimal nutritional status are still unrevealed Present knowledge is inadequate for a comprehensive definition of optimum nutrition and/or optimum health but certainly the nutrition of young and old alike can be vastly improved by better application of existing knowledge In many respects the changes of senescence are primarily consequences of cellular malnourishment

3 Stieglitz, E J Difficulties in the Clinical Recognition of Degenerative Diseases, in Cattell, J Biological Symposia Ageing and Degenerative Diseases Lancaster Pa. Jaques Cattell Press, 1945

atric medicine is not limited to the senile Such would indeed be a sterile field Geriatric medicine is concerned with the aging as well as with those already aged for it is realized that far more can be accomplished for the larger group of senescents than for those fully senile In many respects the two decades from 40 to 60 are the most significant, in these years of later maturity or early senescence we help to determine the future health of the aged Geriatric medicine to be fully effective must be largely preventive medicine[2]

Chronologic age and biologic age are not synonymous and are frequently widely divergent Aging changes vary widely between different persons Furthermore, aging is not symmetric within a single person At various phases of the life span certain structures undergo accelerated alteration as a result of age Thymic atrophy in infancy, hypertrophy of the organs of reproduction at puberty and their involution at the climacteric are illustrative examples Biologic age is asymmetric no person is the same functional age throughout Thus the mensuration of biologic age can never be based on any single or simple criterion Many of those in the fifth and sixth decades of life are prematurely aged some in the seventh and eighth decade are mentally and physically younger than their chronologic years Geriatric medicine must allow for much greater individual variation than is manifest earlier in life In nutrition as in other aspects of the care of aging and aged men and women whether sick or well a high degree of individualization is essential

It has proved practical to assume that geriatric medicine becomes applicable at approximately 40 years of age for it is at this time that the insidious progressive disorders so significant in later years first become manifest It must be kept in mind however that the actual beginnings of such common and important disorders as arteriosclerosis hypertensive disease hypertrophic arthritis and the like occur far earlier than their clinically detectable signs and symptoms It is profoundly

2 Stieglitz E J A Future For Preventive Medicin New York Commonwealth Fund 1945

on a previous asymptomatic impairment. In this connection, geriatric medicine stands in the sharpest contrast to pediatrics for the pediatrician has the right to assume that prior to an acute illness the child was fundamentally well and that therefore all the symptoms *and signs observed are due to the acute disorder* In geriatric medicine one must assume exactly the opposite, that prior to an acute illness the patient was not fully healthy and that many of the evidences of disturbed function may be due to preexistent conditions In many instances these preexistent factors are intimately related to nutrition Because of the element of long duration lesser defects in dietary habits become significant *It is but logical to assume that minor and ill* defined deficiency states are much more frequent in the later years than they are in youth

It must not be assumed however that senescence implies only decline in functional capacity Where some functions diminish others are improved The rate of change of various structures and functional capacity varies considerably in different persons and in the same person It is characteristic that in older men and women the phenomena of disease or of altered function or of reaction to conditions of stress and/or injury are *much less conspicuous than in young persons In geriatric* medicine one must be constantly alert to detect and interpret the significance of subtle and minor variations If one waits until symptoms are obvious it will usually be too late to accomplish as much as should have been accomplished[5]

Factors Affecting Absorption and Transportation of Foods—Certain changes in the alimentary canal and its ancillary structures are significant in the problems of nutrition in later years Loss of teeth interferes with proper mastication an inability to chew properly may *so reduce the tolerance to certain types of foods that* important items are deleted from the dietary Frequently it is possible to correct so-called irritable bowel by insistence on proper dentures Because of painful or missing teeth older persons frequently choose only the softer foods which may lead to difficulties with constipation

The secretion of digestive enzymes and hydrochloric acid by the stomach and the intestinal canal diminishes

5 Stieglitz E. J Therapy of the Aged, M Ann. District of Columbia 17:197 (April) 1948 Geriatrics, J Gerontol. 1:153 (April, pt. 1) 1946

CHARACTERISTICS OF SENESCENT AND SENILE PERSONS AFFECTING THEIR NUTRITION

Obviously it is impossible to discuss here all the many changes which are consequent to the element of time in living Much concerning the complex mechanisms and processes of aging is still unknown [4] We must be content with considering but a few of the more significant aspects of aging which affect nutrition in the second forty years

Individual Variation —An increasing divergence among persons occurs with advancing age. We are today what we are largely because of our yesterdays The older we become the more yesterdays have affected us No two persons experience the same injuries, intoxications, infections, nutritional insults, fatigues or emotional traumas As these inevitable vicissitudes of existence are never identical in character, in severity or in sequence, older persons become increasingly divergent Thus it is essential that there be individualization in analysis of the nutritional status and in any diet therapy Generalizations are dangerous

Some of the individual variations result not only from physiologic changes affected by the mode of living but also from insults and injuries Many of the injuries which are acquired in the course of a lifetime are unavoidable and, in fact may be actually desirable Certain injurious experiences are necessary for the development of powers to protect us from more serious damage Nevertheless every toxic psychic or traumatic injury leaves some residue of scarring behind The detriment may or may not be apparent More frequently it is not Every transient infection affects the parenchymal tissues during the febrile state though one may not see the cloudy swelling which occurs at that time The cumulative effect of these many and varied insults is considerable particularly in older persons Actually it is impossible, even for pathologists, to distinguish with any degree of precision what structural changes in old age are due to aging per se and what are consequent to accumulated injuries [1] Thus, it is often extremely difficult to differentiate the origin of observed clinical phenomena in older patients

Evidences of disordered function may be due to preexistent disorders or to acute maladies superimposed

4 Cowdry E V Problems of Ageing Biological and Medical Aspects, ed 2 Baltimore, Williams & Wilkins Company 1942 Stieglitz [1]

considered a potential cause of arteriosclerotic change, but this has not, as yet, been established in man by controlled observations[6] There is evidence that a high fat intake in the diabetic person contributes to the premature development of arteriosclerosis However, diabetes is a general metabolic disorder, recent observations have indicated that in diabetic patients maintained on balanced normal diets arteriosclerotic change is much more rapid than in nondiabetic persons[7]

Hypertensive arterial disease interferes most decidedly with the nutrition of the tissue cells It must be emphasized that distal to arteriolar constriction the circulation is impaired Capillary stasis creates local impairment of nutrition and the oxygen supply Diminished capillary permeability may add to impaired renal efficiency in enhancing accumulation of detrimental metabolic debris in the tissue interstices The gradual diminution of renal efficiency not necessarily to the point of renal decompensation and therefore the development of clinically obvious uremia makes imperative the desirability of a liberal fluid intake in later years It is more work for the kidneys to secrete a small volume of highly concentrated urine than a larger volume of dilute urine The chronically impaired kidney of later maturity whether due to the vascular changes common with aging or to previous nephritis, requires a larger fluid intake and therefore larger urinary output in order to eliminate the metabolic debris adequately[8] The concept that a liberal intake of water in one form or another is hazardous because of the strain assumed to be placed on the aging myocardium is no longer valid[9]

Metabolic Factors With normal aging there is a gradual diminution in the homeostatic efficiency of the organism This impairment may be accelerated by

6 Steiner A and Domanski B Serum Cholesterol Level in Coronary Arteriosclerosis Arch Int Med **71** 397 (March) 1943

7 Richardson, R and Bowie M A. Diabetes Mellitus as Observed in One Hundred Cases for Ten or More Years Am J M. Sc **208** 1 (Jan) 1945 Kimmelstiel P and Wilson, C Intercapillary Lesions in the Glomeruli of the Kidney Am. J Path **12**: 83 (Jan) 1936 Laipply T C. Eitzen O and Dutra, F R Intercapillary Glomerulosclerosis Arch Int Med. **74** 354 (Nov) 1944 Goodof I I Intercapillary Glomerulosclerosis Ann Int Med **22**: 373 (March) 1945

8 Stieglitz E J Abnormal Arterial Tension edited by M Fishbein New York National Medical Book Company Inc. 1935

9 Schemm F R A High Fluid Intake in the Management of Edema Especially Cardiac Edema I Details and Basis of Regime Ann Int. Med. **17** 952 (Dec.) 194 II Clinical Observations and Data, ibid. **21** 937 (Dec) 1944 Stieglitz.[1]

with advancing age In the eighth and ninth decades an almost complete achylia is usual The secretion of trypsin and pepsin is likewise diminished The actual volume of all the alimentary secretions is lessened Therefore considerable interference with the digestion of foods is to be anticipated Chronic cholecystitis or impairment of function without active inflammation interferes with the utilization of fats, their ingestion may account for considerable flatulence and discomfort In such circumstances, unless the diet be fortified with the fat soluble vitamins from sources other than the natural fats, a deficiency due to spontaneous avoidance of fatty foods is not at all unusual Atrophy of the alimentary mucosa with diminished vascularity makes the senile bowel more vulnerable to trauma and may impede absorption Diminished secretion of mucus which normally serves as a lubricant in the lower intestinal canal contributes to the tendency to impaction and constipation Because of interference with absorption, it is often desirable to prescribe larger quantities of specific food substances indicated to replace deficiencies than would be theoretically necessary With inefficient absorption one must allow for wastage

Transportation of absorbed food elements from the intestinal canal to the tissues is often adversely affected by the changes in the circulatory apparatus which are common with advancing age Cardiac inefficiency, with resultant hypostasis reduces the supply of oxygen to the tissue cells as well as interfering with the removal of metabolic debris Oxygen inadequacy may be regarded as a special type of nutritional deficiency Arteriosclerotic changes roughly parallel advancing age in man However arteriosclerosis may occur in persons as young as 35 to 40, and it must not be assumed that vascular depreciation is an inevitable concomitant of age Age per se is a contributing and not the primary factor in the development of arteriosclerosis That nutritional factors play a significant role in the causation of this common and most important disorder is unquestioned though thus far there is much confusion of the interpretation of clinical and experimental observations The concept that a liberal protein intake contributed to this disorder is no longer valid, Eskimos living almost solely on animal tissue and therefore on a very high protein diet do not show any increased incidence of either renal or vascular disease Fat has been

organism are prepared for the riddance from the body of acid substances It was demonstrated years ago that the early Sippy ulcer management with sodium bicarbonate not infrequently induced alkalosis in elderly patients [1] The ill consequences of hypoproteinemia in causing edema, poor wound healing retarded bone healing decreased resistance to generalized infection and the like are much more marked in older persons [13] The *maintenance of plasma protein* is an absolute necessity [14]

In man the basal metabolic rate appears to diminish with age This is not the case with dogs or with rats, as demonstrated by extensive experimental studies In some respects, the diminution in metabolic rate with advancing age in man is unique for it is the only physiologic constant for which we make correction for age in the calculation of normal levels It still remains to be demonstrated whether this decline in caloric utilization and oxygen consumption with advancing age is necessarily desirable Just because it occurs in the majority certainly does not prove its desirability We know that most persons tend to gain weight after their full maturity but recent studies prove that this gain is undesirable and affects longevity adversely However from the clinical point of view the fact that the basal rate does decline with age and that this diminution is of considerable magnitude is important because the older person needs less calories even if continuing to be active It is possible that the change in thyroid activity as indicated by the changes in basal metabolic rate affects cholesterol metabolism and thereby may play a role in the development of arteriosclerosis [15] Further study in the interrelationship of thyroid activity arteriosclerosis and cholesterol metabolism is needed At the present the data are too confusing to warrant final interpretation

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12 Stieglitz E. J Alkalis and Renal Injury Arch. Int. Med. **41**: 10 (Jan) 1928

13 Filbback F C. Surgery in the Aged Clinics **4**: 1250 (Feb) 1946 Zintel H A. The Role of Nutrition in Preoperative and Postoperative Care Am J M Sc **207** 204 (Feb) 1944

14 Madden S C and Whipple, G H Amino Acids in the Production of Plasma Protein and Nitrogen Balance, Am. J M Sc. **211**: 149 (Feb) 1946 Maycock R L. Koop C E. Riegel C Kough N T. and Starr I Convalescence from Surgical Procedures Am J M Sc. **212**: 591 (Nov) 1946

15 Rosenkrantz, J A and Marshall C Basal Metabolic Rate in Hypertensive Vascular Disease Arch. Int. Med. **80** 81 (July) 1947 Kirk, E Chieffi M. and Kountz W The Correlation Between Thyroid Function and the Incidence of Arteriosclerosis, J Gerontol. **4**: 212 (July) 1949

accumulated injuries of previous disease It is well known that the internal milieu of the organism remains nearly constant throughout the life span and the ranges of almost all the so called physiologic constants such as temperature pulse rate, concentrations in the blood of glucose, protein, calcium and the like, are about the same at age 80 as at 8 Nevertheless, the ability to maintain such constancy depreciates with advancing age Tolerance for stresses of all sorts is diminished, older persons do not adjust as well as younger adults to extremes of temperature and dehydration to starvation, to excesses in carbohydrate intake and the like The early *lowering of efficiency is revealed* only by observation under conditions of stress

Because the glucose tolerance test creates physiologic stress it is particularly valuable *in the evaluation* of health in later years The curve obtained in the glucose tolerance procedure in older persons frequently resembles that seen in younger diabetic patients The aging person does not respond well to a rapid absorption of glucose[10] Similarly the older person does not tolerate a lowered blood sugar content, whether the result of starvation or of hyperinsulinism Soon after the introduction of insulin into the management of diabetes mellitus it was observed that elderly diabetic persons, when precisely controlled to maintain a perfectly normal blood sugar at all times, frequently had circulatory difficulties A low blood sugar content (and this may not be so low as to be below the average normal range but only relative for the individual) may induce episodes of acute angina pectoris[8] Glucose is a major source of cardiac energy[11]

Similarly the older person does not tolerate dehydration or very rapid introduction of fluids The acid base balance is likewise less well maintained With aging there develops an increasing inability to handle excesses of alkali, excesses of acids are more efficiently disposed of because the normal physiologic mechanisms of the

10 Smith L E and Shock N W Intravenous *Glucose Tolerance* Tests in Aged Males J Gerontol 4 27 (Jan) 1949

11 Smith F M, Gibson R B and Ross N G Diet in the Treatment of Cardiac Failure J A M A 88 1943 (June 18) 1927 Middleton N S and Oatway W H Am J M Sc. 181 39 (Jan) 1931 Soskin S Katz L H Strouse, S and Rubinfeld, S H Treatment of Elderly Diabetic Patients with Cardiovascular Disease Available Carbohydrate and Blood Sugar Level Arch Int Med 51:122 (Jan.) 1933 Harrison T R and Finks R M Glucose Deficiency as a Factor in the Production of Symptoms Referable to the Cardiovascular System, Am. Heart J 26:147 (Aug) 1943

Habits may last longer than life itself, for they may be transmitted from one generation to the next It is extremely doubtful, for example whether obesity is primarily an inherited characteristic in the purely genetic biologic sense. The child who grows up in a family where the parents are obese by reason of overeating acquires the habit of eating excessively The longer habits have been indulged in the more rigidly they become fixed [21]

Dietary habits are affected by many elements Cost of food is often the most significant factor Secondly, the ease of preparation is significant for older persons particularly when they have to prepare their own foods The elderly are prone to rely largely on packaged foods, and particularly on bakery goods and consequently often develop an asymmetric dietary The tendency of older persons is to eat excessive amounts of carbohydrate and insufficient protein [19] The ease with which food is consumed plays a role in selection of the diet of an older person As previously mentioned inadequate dentures tends to limit the diet to softer foods

Psychologic Factors Psychologic factors play an important role in the determination of a proper dietary Anxieties, especially if long continued and habitual, may lead either to a serious anorexia or to excessive consumption of foods with obesity as a consequence Anorexia is not uncommon when the will to live" is weakened by long distressing illness and disablement. In such circumstances small frequent feedings are often much better tolerated than larger meals Where the appetite is poor one of the most important considerations is that the food supplied be easy to eat Patients will sometimes refuse a delicacy such as a squab but eat a simple hamburger because the latter is already ground up and requires a minimum amount of effort for consumption Such persons are not interested enough in eating to take the trouble to pick the meat off a squab Considerable food can be introduced in the beverage form if the appetite is extremely poor Frequently liberal amounts of the vitamin B complex are given in an attempt to encourage the appetite in such circumstances

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21 Stieglitz E. J *The Second Forty Years*, Philadelphia, J B. Lippincott Company 1946.

Impaired uric acid metabolism increases in frequency with age. Gout is by no means limited to the elderly and has been reported in extreme youth, but its frequency definitely increases after the peak of maturity. Thus far there have not been developed any generally applicable clinical tests for measuring the ability of the organism to handle known amounts of purines. But when and if a clinical test procedure is developed, we may anticipate observations indicating a gradual decline in ability to utilize purines without accumulation of uric acid with advancing age. Acute episodes of gout are precipitated by less and less noteworthy indiscretions as the gouty patient ages.

Variations in mineral metabolism with age are not fully understood. Loss of calcium and phosphorus as a result of alimentary disturbances in the aged, apparently are factors in the characteristic atrophy of bone seen in the senile person. Steindler stated[16] that one of the most common causes of inadequate utilization of ingested calcium is lowered gastric acidity and hepatic and pancreatic insufficiency, so frequently seen in the aged. The immediate result of these deficiencies is reduced fat absorption with the inability to absorb the fat-soluble vitamin D essential for the absorption and utilization of ingested calcium. Recent experimental studies have indicated that in older animals it is extremely difficult to maintain calcium balance.[17] These observations are also confirmed by recent studies of the nutritional status and requirements of 100 women 40 to 75 years of age.[18] The dietary calcium requirements of older women appear to be higher than standards proposed for adults.[19]

Habits. Habits good, bad or indifferent are acquired and fixed by repetition over a period of time. Duration is an absolute requisite. Thus age is a significant element in habit formation. Habits of eating play a most significant role in nutritional problems. Habits are probably one of the greatest obstacles in the path toward obtaining an optimum diet by the majority of persons.[20]

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16 Steindler, A. Diseases of the Bones, in Stieglitz,[1] chap 43.
17 Kane, C. G., Lovelace, F. E., and McCay, C. M. Dietary Fat and Calcium Wastage in Old Age, J. Gerontol. 4: 185 (July) 1949.
18 Ohlson, M. A., Roberts, P. H., Joseph, S. A., and Nelson, P. M. Dietary Practice of One Hundred Women from Forty to Seventy-Five Years of Age, J. Am. Dietet. A. **24**: 286 (April) 1948.
19 Roberts, P. H., Kerr, C. H., and Ohlson, M. A. Nutritional Status of Older Women, J. Am. Dietet. A. **24**: 292 (April) 1948.
20 Carlson, A. J. Some Obstacles in the Path Toward Optimum Diet, Science **97**: 385 (April) 1943.

fluid about 20 per cent Though the over-all volume of this fluid is relatively constant water is being utilized in various ways and is thus in a state of flux The magnitude of this utilization is impressive. It has been estimated, for example that in twenty four hours there are from 500 to 1 500 ml of saliva secreted from 1 000 to 2 500 ml of gastric juice, from 100 to 400 ml of bile and from 700 to 3 000 ml of intestinal secretions Furthermore Smith has presented data to indicate that as much as 170 liters of water are filtered from the plasma in twenty four hours by the kidneys Of course most of this is reabsorbed by the convoluted tubules Even relative dehydration can have profoundly deleterious consequences Excessive ingestion of water is rare The ability of the organism to eliminate excesses of water is far greater than its ability to conserve fluids when an adequate intake occurs

Practically all water is normally obtained by the oral route Some water of course is derived from foods which are not liquid at the time of their ingestion However the water derived from solid elements of the diet should not be calculated as far as the water intake is concerned because the insensible loss of fluid through respiration and continuous perspiration exceeds that which is obtained from this source [23] The total intake of beverage fluids should be such that the twenty-four hour urinary volume is a minimum of 1 500 ml In hot weather this may mean a fluid intake of 3 liters or more but in ordinary cool weather with moderate activity an intake of approximately 2 liters is optimum In the older person it may be desirable that the fluid intake be spaced with small amounts taken at relatively frequent intervals rather than large quantities at any one time In these circumstances there is less strain on the absorptive mechanism of the intestinal canal and on the circulatory distribution of the fluid Persons who because of a cystocele or prostatic obstruction are bothered with nocturia should avoid consuming the major portion of their fluids in the latter part of the day Many older individuals complain that they do not like water It is feasible for them to consume flavored beverages such as ginger ale tea either hot

2 Smith H. W The Physiology of the Kidney New York, Oxford University Press 1937

23 Peters, J P Body Water The Exchange of Fluids in Man. Springfield, Ill., Charles C Thomas, Publisher 1935

In the middle years of senescence or later maturity obesity is a much more frequent problem than undernutrition It must be remembered that both are forms of malnutrition Anxiety or discontent is at the back of most instances of overeating Eating may be an escape mechanism, it is a source of considerable physical pleasure and permits the individual to find calm because digestion and a full belly induce drowsiness and lessened awareness of annoyances [21] Few obese senescents survive to become senile [1]

Occasionally one sees a truly aged patient who gives a history that for many years he or she has lived on an outrageously unbalanced diet which should, according to our more recent scientific knowledge have led to serious nutritional deficiencies Nevertheless, the mere fact of survival to ripe senility is convincing evidence that perhaps the scientifically illogical diet is not as bad as we might think The habits of the aged are to be respected experience may have taught them what they as individuals can tolerate The characteristic of individual variability increasing with the years must never be forgotten It is important not to insist on abrupt changes in habits of aged patients Unwise habits can be modified slowly but sudden and radical changes in the mode of life are physically upsetting as well as emotionally disturbing Furthermore if the advice regarding dietary habits is too restricted or too much at variance with the established mode of life, the patient will not follow the therapeutic suggestions and nothing whatever is accomplished

SPECIFIC NUTRITIONAL NEEDS

Not all the specific nutritional needs of older persons are known Basic nutritional requirements are essentially similar to those of a younger adult, with certain modifications introduced by aging and chronic metabolic disorders By grouping the important nutritional elements the discussion of specific nutritional needs may be facilitated and clarified

Water—The habit of ignoring water as an element of diet is to be deplored Unfortunately in many discussions of nutrition consideration of water is omitted Yet of the total weight of the human body some 70 per cent is water The intracellular water is about 50 per cent of the total body weight and the extracellular

Obesity is almost invariably due to an excessive consumption of calories [5] Though glandular disturbances including those of the climacteric, have been blamed for many instances of obesity, the fact remains that overweight persons eat more than they require It is doubtful if more than 1 per cent of instances of obesity in later years are attributable to endocrine disorders The control of obesity involves two points of attack (1) prescription of a dietary with sufficient calories to maintain vigor and activity but less than that which is required to maintain the excessive weight and (2) the control of appetite so that this diet may be followed for sufficient time to permit of reduction to normal weight In the adjustment of the diet the major restrictions in calories should be in carbohydrates and fats Proteins should not be limited and are often best increased Control of the appetite is often greatly assisted with the oral administration of 5 mg of dextro amphetamine approximately fifteen minutes to one half-hour before meals No detriment has been observed from the utilization of this drug [26] Exploration of the psychologic factors responsible for the excessive appetite is an important factor in the treatment of obesity [27] Thyroid substance is rarely indicated The indiscriminate prescription of thyroid preparations is most unwise and has resulted in unnecessary injury Not infrequently administration of thyroid increases the appetite excessively, thus making weight reduction more difficult

It is extremely important that weight reduction in persons in the second forty years be gradual A weight loss of approximately a pound (0 5 Kg) a week or a maximum of 5 pounds (2 3 Kg) a month is as rapid as is usually advisable However it must be kept in mind that with the gradual reduction of approximately 5 pounds a month it is possible for the patient to lose 60 pounds (27 2 Kg) within the year The reasons for insisting on a gradual long term program of weight reductions are several In the first place rapid weight losses are usually quickly regained because patients do not change their habits of eating Gradual weight

5 Newburgh, L. H Obesity Arch. Int. Med. 70 1033 (Dec.) 1942

6 Colton, N H Segal, H I Steinberg A. Shechter F R., and Pastor N The Management of Obesity with Emphasis on Appetite Control Am. J M Sc. 206 75 (July) 1943

Freed, S C Psychic Factors in the Development and Treatment of Obesity J A M A 133 369 (Feb 8) 1947

or cold coffee, soups, fruit juices and the like It is not difficult to make fluids interesting to the palate.

Edema, whether due to nephrosis or to cardiac incompetence, does not justify the radical restriction of water to a minimum Edema fluid is toxic[8] Edema will accumulate whether water be ingested or not During the subsidence of edema, whether spontaneously or from diuretic medication, it is important to cover this diuresis with an adequate water intake else the patient becomes severely intoxicated by the liberation of toxic metabolic debris which has accumulated in the edema stored in the tissues Many times the cardiac invalid is more severely ill and in greater jeopardy during the subsidence of anasarca than during its accumulation[4]

In extremely hot weather not only is an increased amount of water a necessity but also additional intake of sodium chloride Additional salt should be given at meals and not as a separate item The studies of the Army indicate that approximately 12 Gm of salt is required for those in hot climates working at sedentary occupations Those working hard for eight hours daily require 24 Gm but such quantities would rarely apply to older persons

Calories—The detrimental effects of obesity in the later years of life can hardly be overemphasized Extensive actuarial studies of the effects of abnormal weight on expected mortality in persons otherwise normal reveal that those 15 to 24 per cent overweight present a mortality of 144 per cent of that expected and those 25 per cent or more overweight show a mortality of 174 per cent of the expected rate In the presence of cardiovascular disease the hazards of overweight are even more marked If the death rate of cardiovascular patients of normal weight is taken as 100 per cent the mortality rate for those overweight is found to be 162 per cent of normal whereas for those underweight the death rate is only 77 per cent Similar consequences occur when obesity complicates diabetes mellitus The mortality from diabetes mellitus is increased to 250 per cent over that which occurs in those of normal weight when obesity is a factor[21]

24 Stieglitz, E. J Cardiac Failure Ann. Int. Med. 6 406 (Sept.) 1932.

a valuable source of protein but also a major source of calcium Skim milk may be preferable to whole milk as a source of extra protein, especially if one wants to avoid increasing the fat intake Dried skim milk preparations particularly those fortified with additional iron and vitamins are of considerable value in the maintenance of good nutrition in the senile person Other significant sources of protein are cheese and lean meats Nuts are relatively poorly tolerated by the majority of older persons particularly if they are not properly chewed The value of eggs in the dietary of the older person is open to question at the present moment because of the controversy concerning the hazards of cholesterol ingestion

The role of nutrition and particularly of adequacy of protein in the preoperative and postoperative care of the elderly is extremely important [8] In acute surgical emergencies intravenous administration of hydrolyzed amino acids is entirely justified and often invaluable but in the long term nutritional problem of protein depletion in older persons protein hydrolysates are largely unnecessary Almost all the protein hydrolysates prepared for oral administration are so extremely unpalatable that it is difficult if not impossible for the patient to continue their ingestion over a long enough period and in sufficient quantities to be fundamentally beneficial There is no reason whatever why the usual protein foods such as milk products cannot be employed to maintain adequate protein intake

The metabolic requirements of the older person are similar to those of a younger person namely a minimum of 1 Gm of protein per kilogram of body weight per day However many elderly patients are in a state of negative nitrogen balance and ingestion of 2 Gm of protein per kilogram of body weight may be necessary to produce a positive balance On such a liberal protein intake a positive balance may be maintained for as long as a year showing the extent of the previous tissue protein depletion [29] Any loss of protein

28. Tui, C. Th Value of Protein and Its Chemical Components in Surgical Repa Bull. New York Acad. Med. 21 631 (Dec.) 1945 Fibback, F C. Principles of Geriatric Surgery in Stieglitz,[1] chap 7 Elman, R. Parenteral Alimentation in Surgery with Special Reference to Proteins and Amino Acids New York, Paul B Hoeber Inc., 194[illegible]

29 Kountz W B Hofstatter L., and Ackermann P Nitrogen Balance Studies Under Prolonged High Nitrogen Intake Levels in Elderly Individuals, Geriatrics 3: 171 (May) 1948

reduction permits of the development of new eating habits At the end of six months or a year of dietary control the person does not tend to regain the weight lost Secondly, with slow but persistent reduction the patient does not complain of a sense of weakness or exhaustion Wrinkling of the skin is avoided by slow slimming This is important to middle aged and elderly alike Weight reduction in the mature adult requires patience and persistence on the part of the physician as well as of the patient Education and constant encouragement however, can accomplish much [1]

Proteins —The elderly are prone to suffer from protein deficiency more than from any other form of deficiency [18] Inadequacy of protein is a significant factor in the pathogenesis of tissue wastage, anemia and edema Mild deficiencies may be manifested primarily by a sense of habitual fatigue Plasma protein determinations on blood from older persons frequently reveal a moderate degree of insufficiency It is not difficult to determine the degree of protein deficiency of the serum protein concentration Normally, the serum protein should be about 7 Gm per 100 ml To illustrate the calculation necessary to determine the total protein deficiency we may take as an example an instance wherein the serum protein is 5 Gm per 100 ml This represents a deficit of 2 Gm per 100 ml of serum The plasma volume is 5 per cent of the total body weight Thus if the patient weighs 70 Kg (154 pounds), we know that the plasma weighs 3 5 Kg, or is approximately 3 500 ml in volume Therefore a deficiency of 2 Gm per 100 ml multiplied by 35 equals a total deficit of 70 Gm in plasma protein For each gram of plasma protein reduced from the normal it is estimated that there exists a 30 Gm depletion of the tissue protein reserves Therefore, 70 times 30 equals 2,100 Gm as the depletion of tissue protein Thus the total protein deficiency is 2 170 Gm If the deficit is to be restored, it is necessary that a total ingestion of something over 2 000 Gm of protein be added to the usual daily requirement of 1 Gm per kilogram per day These 2 Kg of additional protein may be spread over as many days as is deemed advisable in making up the deficiency

Unfortunately the majority of older persons dislike or resent the prescription of milk Milk is not only

a valuable source of protein but also a major source of calcium Skim milk may be preferable to whole milk as a source of extra protein especially if one wants to avoid increasing the fat intake Dried skim milk preparations particularly those fortified with additional iron and vitamins are of considerable value in the maintenance of good nutrition in the senile person Other significant sources of protein are cheese and lean meats Nuts are relatively poorly tolerated by the majority of older persons particularly if they are not properly chewed The value of eggs in the dietary of the older person is open to question at the present moment because of the controversy concerning the hazards of cholesterol ingestion

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28. Tui, C. The Value of Protein and Its Chemical Components in Surgical Repair Bull. New York Acad. Med 21 631 (Dec) 1945 Fishback F C Principles of Geriatric Surgery in Stieglitz chap 7 Elman, R Parenteral Alimentation in Surgery with Special Reference to Proteins and Amino Acids New York, Paul B Hoeber Inc. 1947

29 Kountz W B Hofstatter L., and Ackermann P Nitrogen Balance Studies Under Prolonged High Nitrogen Intake Levels in Elderly Individuals, Geriatrics 3: 171 (May) 1948

through persistent proteinuria demands compensatory increase in the protein intake

Carbohydrates—The hazards of either excessively high blood sugar levels or reduction of the blood sugar to below optimum levels in the older person have been mentioned previously Adequate carbohydrates to balance the diet and, of course, appropriate restrictions for the diabetic patient are in order

Fats—The controversy as to whether arteriosclerosis and fatty degeneration of the liver, both conditions likely to be encountered with advancing years are due in any respect to a diet excessively rich in fats and cholesterol is still unsettled There are those who maintain that high fat diets contribute decidedly to the formation of arteriosclerotic change The low incidence of arteriosclerosis in the Chinese and the decrease in incidence of this disorder in Germany during the years of fat shortage following World War I are considered to be significant in this connection [30] On the other hand studies in the relationship of prolonged increases of cholesterol in the diet to the incidence and severity of coronary arteriosclerosis indicate that there was no parallelism between the two The nutritional role of cholesterol in the genesis of human atherosclerosis is of doubtful significance [31] There is, however no doubt that there exists a relationship between obesity, which may be due to the excessive ingestion of fats as well as of other sources of calories and the incidence and severity of atherosclerosis [32]

Recent experimental work with animals has shown that certain types of fatty liver cirrhosis are affected by a faulty diet and prevented to a large extent by adequate amounts of dietary choline or the milk protein casein [33] In addition to choline methionine and inositol

30 Moreton J R. Atherosclerosis and Alimentary Hyperlipemia, Science **106**: 190 (Aug 29) 1947

31 Shaffer C. F The Nutritional Role of Cholesterol in Human Coronary Arteriosclerosis, Ann Int Med. **20**: 948 (June) 1944

32 Wilens, S L Bearing of General Nutritional State on Atherosclerosis, Arch. Int. Med **79** 129 (Feb) 1947

33 Blumberg H and McCollum E V The Prevention by Choline of Liver Cirrhosis in Rats on High Fat Low Protein Diets, Science **93** 598 (June 20) 1941 Daft F S Sebrell W H and Lillie R D Production and Apparent Prevention of a Dietary Liver Cirrhosis in Rats Proc. Soc. Exper Biol & Med **48** 28 1941 Patek A J Jr and Post, J Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex, J Clin Investigation **20** 481 1941 Engel R W Relation of B Vitamins and Dietary Fats to the Lipotrophic Action of Choline J Nutrition **24** 175 1942

are significant factors in the metabolism of cholesterol These agents may assist decholesterolization It has been reported by Herrmann that inositol in doses of 2 Gm per day for twenty five to thirty days reduced the cholesterol and cholesterol esters as much as 14 per cent[34]

It is becoming increasingly evident that there exists a close relationship between high serum cholesterol levels and coronary arteriosclerosis[35] Morrison has reported that the cholesterol content of coronary arteries in patients who died from acute coronary occlusion and myocardial infarction is often four times as great as the average cholesterol content of coronary arteries of control patients of comparable age[36] It is the considered opinion of many cardiologists that the greatest hope of preventive measures in the area of arteriosclerotic heart disease lies in the nutritional control of cholesterol metabolism

The full significance of inositol and other lipotrophic enzymes is as yet undetermined[37] The role of thyroid activity in connection with cholesterol metabolism cannot be ignored This whole area of nutritional research is advancing so rapidly that concepts cannot be crystalized sufficiently to permit of sound, confirmed clinical recommendations at the present moment

Minerals—Most of the minerals required by the body are available in ample quantities However both cal cium and iron are frequently deficient Not only is calcium frequently inadequate in the diet of elderly persons in part because of their dislike for milk and milk products but it has been demonstrated that the older organism has difficulty in the absorption and utilization of calcium[38] Clinical studies have shown

34 Herrmann, G R Cholesterol Levels in Various Diseases and the Effects of Decholesterizing Agents Texas State J Med 42:260 (Aug) 1946 Some Experimental Studies in Hypercholesteremic States Exper Med. & Surg 5 149 (May Aug) 1947

35 Steiner A Significance of Cholesterol in Coronary Arteriosclerosis, N Y State J Med 48:1814 (Aug) 1948

36 Morrison, L M Hall L and Chavez A L Cholesterol Metabolism Blood Serum Cholesterol and Ester Levels in Two Hundred Cases of Acute Coronary Thrombosis Am. J M Sc 216:32 (July) 1948 Morrison L. M Chavez A L Hall L and Gonzales W The Role of Lipoid Metabolism in Production of Coronary Arteriosclerosis and Atherosclerosis, Am J Med 6:388 (March) 1949

37 Woolley D W The Nutritional Significance of Inositol J Nutrition 28:305 (Nov) 1944

38 Kane G G and McCay C M Calcium Requirements of Old and Young Hamsters and Rats J Gerontol 2:244 (July) 1947

also that it is more difficult to maintain calcium balance in older persons [19] The major food sources of calcium are milk, cheese, ice cream, green vegetables and legumes As time is an extremely significant element in the development of gradual and insidious deficiencies in nutrition, it may require a considerable period to restore calcium balance in older patients who have been gradually depleting their reserves over many years The patient should be made aware of the inevitable slowness of correcting long-standing deficiencies

The recommended allowance for iron for an adult is approximately 12 mg per day Habitual intakes below this level are extremely common Moderate anemias are almost the rule in elderly persons It does not suffice in these instances to encourage an increased intake of milk for milk is ordinarily deficient in iron, though an extremely valuable food in other respects One dried milk preparation has been fortified with the addition of iron so that this deficiency is corrected Clinical experience reveals that a great majority of elderly persons require supplemental administration of iron salts of one form or another [39]

Vitamins—Because the role and importance of the various vitamins in human nutrition have been discussed elsewhere in the present series, this discussion is intentionally brief Of particular interest to those whose problem is the nutrition of the elderly is the fact that low grades or minor degrees of vitamin deficiency can be assumed to be the rule rather than the exception Slight inadequacy of intake over a long period or excessive utilization because of recurrent infections and intoxications or impairment in absorption may all contribute to chronic vitamin inadequacy It has been shown [40] that liberal additions of the vitamin B group and ascorbic acid to the dietary of older persons can make for great improvement in general vitality and vigor In most instances of such deficiency states in elderly persons there exists a general inadequacy other than insufficiency of any one element The importance of folic acid, as well as iron in the maintenance of an adequate hemoglobin content in elderly patients must not be forgotten Rarely is the diet so specifically

39 Sebrell W H Malnutrition in Stieglitz [1] chap 11

40 Stephenson W Penton C and Korenchevsky V Some Effects of Vitamin B and C on Senile Patients Brit M J 2:839 (Dec. 13) 1941

asymmetric that there is a gross and conspicuous deficiency of one item without depletion of the other elements

Vitamin supplementation through special preparations or, in severe cases, by the use of parenteral injection may be necessary in addition to a well planned adequate diet Some studies indicate that the aged require a larger vitamin intake than the average normal adult,[41] whereas other investigations [42] have revealed no particular difference in requirements Because of difficulties in absorption and utilization it is felt that the usual normal intake for an adult can well be doubled for those in later maturity or in actual senility The balance between the various vitamins should be preserved at approximately the usually recommended level There is great need for extensive studies of the specific requirement in later maturity

Bulk—The older bowel as well as that of the younger person requires an adequate amount of soft bulk in order to prevent constipation and the development of hard dry stools The senile intestinal mucosa does not tolerate roughage The roughage from bran and the scratchy fibers of items such as celery and hulls of corn must be distinguished from soft bulk Frequently, the simplest method of explaining this distinction to patients is to point out that any fruit or vegetable which can be strained through a colander will contain no roughage *though such foods need not be actually pureed* Major vegetable sources of soft bulk are the roots such as beets turnips parsnips carrots and the leaves such as spinach lettuce cauliflower brussel sprouts and broccoli The stalks such as celery and rhubarb are rather too rough for many aged bowels The seeds peas and beans offer little bulk though their nutrient value is unquestioned Corn is in most instances far too irritating Control of the bulk in the diet, as well as all other items, must be highly individualized in geriatric nutrition

Accessories—Excesses of condiments and spices particularly those which are prone to burn the tongue

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41 Rafsky H A and Newman B Vitamin C Studies in the Aged Am. J M Sc. **201** 749 (May) 1941 Vitamin B Excretion in the Aged Gastroenterology 1:737 1943 Relationship of Niacin (Nicotinic Acid) to Porphyrinuria in the Aged Am J M Sc **203** 209 (Feb) 1943

42 Horwitt, M K, Liebert E, Kreisler O and Wittman P Bulletin 116 Investigations of Human Requirements for B Complex Vitamins, National Research Council June 1948

such as pepper, mustard, horseradish, Worcestershire sauce and chili con carne, are undesirable for aged persons because not only are they irritating to the intestinal tract but they contribute to vascular and renal irritation [8]

The importance of an adequate fluid intake has already been emphasized Coffee and tea are not contraindicated except in specific illnesses or idiosyncrasies Recent studies have indicated that the administration of coffee throughout the life span of experimental animals has no ill effect whatsoever [43] Frequently, the desirable morning diuresis and stimulation of caffeine is highly profitable to the older persons When insomnia is a problem caffeine in any form late in the day is to be discouraged The habits of the aged are to be respected

Alcohol is a vasodilating substance It is of considerable assistance in the management and control of arteriosclerotic change in elderly persons [44] In my opinion the judicious use of whisky or other spiritus liquors is therefore indicated in the management of many aged patients Alcohol in moderation supplies quick fuel, relaxes tensions and tends to increase the appetite A glass of wine or a highball before dinner and another at bedtime is often most constructive in increasing vigor and endurance in the elderly

SUMMARY

Science is not static Our knowledge of nutrition and understanding of gerontology or the science of aging are advancing rapidly [45] Geriatric medicine is daily learning more and more about the changing capacities and limitations and therefore needs of aging men and women With every increment in knowledge certain concepts must be revised and some discarded Thus, the conclusions and suggestions presented herewith are to be considered tentative and open to revision However while we discover new facts we must use our existing knowledge as effectively as possible even though we know it to be incomplete and tentative It is comforting to keep in mind that awareness of ignorance is a necessary prelude to learning

43 Sperling G Loosli J K Barnes L L. and McCay, C. M The Effect of Caffeine Human Diets and Inheritance upon the Life Span of Rats J Gerontol 1 426 (Oct) 1946

44 Wright I S Arteriosclerosis in Stieglitz,[1] chap 29

45 Stieglitz E. J The Orientation of Geriatrics Geriatrics 4:127 (May June) 1949

The essentials of good nutrition in geriatric medicine must include consideration of the following principles

1 Moderation Excesses are as undesirable as deficiencies Both induce malnutrition It is often most helpful for older persons to eat small quantities frequently rather than to attempt large meals

2 Individualization Individual variation increases with advancing years Generalizations and routine dietary programs are unwise Many variable factors, such as digestive and circulatory efficiency, habits dentures and the like affect the prescription of diet in the elderly

3 Water The importance of an adequate fluid intake must never be forgotten

4 Maintenance of hemoglobin content Anemia even if minor is immensely more significant in later years than in youth for the ability to compensate for inadequacy declines In the presence of any circulatory handicap (arteriosclerosis hypertension or cardiac impairment) the quality of the circulating medium assumes a role of major importance Optimum hemoglobin concentrations should be the objective, the average does not suffice

5 Balance in dietary is as important here as at any age Asymmetry in utilization however may alter the optimum proportions of various elements in contrast to the usual standards for young adults Protein iron and calcium are the elements most likely to be inadequate in spontaneously selected dietaries among the aged

6 The focus of attention must be on the person rather than on his disease or diseases The human being is indivisible psyche and soma are one Insulin does not suffice for the anxious diabetic patient nor does equanimity come to the exhausted anemia patient An attitude of constructive prophylaxis is essential to effective geriatric medicine The primary objective is the construction of health to as near the optimum as possible Wise nutrition is a most powerful tool for the attainment of vigor in later years

CHAPTER XVII

NUTRITIONAL NEEDS IN ILLNESS AND DISEASE

GEORGE V MANN
and
FREDRICK J STARE

Physicians are puzzled by the inability of their colleagues who work in investigative nutrition to supply them with the simple accurate statements of the daily requirements of the essential nutrients of a healthy human being To the uninitiated it would seem a straightforward request of easy solution However the elusive mechanisms by which many of the essential nutrients function coupled with a paucity of biochemical technics by which specific deficiencies can be accurately detected have limited these answers to approximations

In laboratory animals when dietary factors can be rigorously controlled and when the use of large numbers of subjects allow statistically sound conclusions, the requirements are reasonably well established for at least a few species The nutritional requirements of the rat for example are known fairly well, but this achievement has required the concerted efforts of hundreds of workers over a period of decades

When one considers the abnormal, that is the diseased person the problem of nutritional requirements becomes more complicated

There can be no question of the environmental importance of diet in fact one can justifiably say that food is the most important environmental factor affecting health The food we eat not only is one of the most continuous elements of our environment but also assumes by far the most intimate relationship with us The food we eat enters and does in fact constitute the very structure of our bodies It has long been apparent that there exists a correlation between the

nutritional environment and the form and capabilities of the individual and of his society It is also an ancient observation that death and disease are guided to a large extent by diet Within modern times irrefutable studies have shown in many parts of the world that diet conditions disease, diet influences growth and development and diet is a decisive factor in determining death rates

Appreciation of the nutritional aspects of disease have been handicapped by two principal concepts (1) The medical profession has been (and unfortunately in most quarters still is) trained to think of nutritional deficiencies in terms of overt and florid physical manifestations for example the flagrant signs of beriberi or scurvy (2) The profitable returns from production and exploitation of nutritionally active substances have caused great pressure to be brought on both the patient and the physician, encouraging them to believe, that many common physical disorders can be prevented and cured by profuse vitamin mineral or protein medication This philosophy exists at the expense of sound food habits in the home and sound nutritional diagnosis and therapy in the hospital and physician's office.

Although there are no established quantitative values for the requirements of the various nutritional substances in diseased states it is possible to arrive at a reasonable dietary treatment of many diseases by an appraisal of experimental laboratory data and of clinical trial and error

Such information as is available concerning the dietary needs of man in illness and disease is largely of two sources (1) directed laboratory studies of diseased animals (including man) with a view to measuring in as objective a fashion as possible the nutritional status and (2) clinical observations either of the response to nutrient supplementations or observations of the effect of an illness superimposed on a prior clinical deficiency state As a corollary to this method is the statistical procedure of comparing morbidity or mortality rates of populations with diverse dietaries

Because the methodology essential to a nutritional point of view and adequate therapy is of relatively modern origin and distinctive character, we shall review the fundamentals

NUTRITIONAL HISTORY

The nutritional status of a patient when first seen is in large part determined by the dietary intake for the preceding months An initial step then in the evaluation of the reciprocal relationships of the present nutritional status and disease is an attempt to establish data regarding the diet history It follows that the diet history is an integral part of the medical history The inadequacy of ascertaining what the patient has eaten at the three immediately preceding meals is apparent It is necessary to determine the food pattern for the preceding weeks and months How often are certain foods—vegetables citrus fruits milk products and meat—consumed per day and per week and in what quantity? For the examiner at least a basic knowledge of food composition of average helping size and of local availability of various foods is of importance.

In the evaluation of the nutritional status of the *patient by means of the history the social history is of* considerable value Frequently there is good correlation between economic income and dietary adequacy Familiarity with racial and religious food taboos, group diet customs and personal idiosyncrasies is valuable Finally, it must be admitted that until the individual physician is convinced of the importance of nutritional environment in conditioning disease his histories will continue to be inadequate

With a good diet history at hand, the physician with an elementary knowledge of normal nutritional requirements will be able to evaluate the patient s dietary A convenient guide is the National Research Council s Recommended Dietary Allowances' It is probably sufficient to be able to say that a particular patient has received adequate marginal or inadequate quantities of various nutrients such as protein calcium riboflavin or vitamin A With this accomplished the physician is able to correlate the physical manifestations of disease present with the diet history and to design his therapy

accordingly Clinical specialists in nutrition are skeptical of the value in medical practice of elaborately computed estimates of the amount of each dietary essential consumed daily

PHYSICAL EXAMINATION

Medical literature abounds with real or supposed physical manifestations of specific nutritional deficiency states Abnormalities of skin, mucous membranes hair, nails and neurologic signs are frequently attributed to various deficiencies Although these signs may be sufficiently demarcated in the rare case to allow objective evaluation characteristically the physical signs of deficiency states are nonspecific and multiple. The manifestations of the majority of deficiency states complicating disease are far more subtle than is commonly believed It is not the purpose of this paper to discuss the physical signs (or symptoms) associated with poor nutrition

LABORATORY EXAMINATION

A series of biochemical technics have been developed which are of some assistance in the evaluation of the nutritional state when a good laboratory is available In the blood, total protein, albumin globulin, hemoglobin iron ascorbic acid vitamin A and carotene, as well as some other nutrients, can be measured Blood volume can also be determined This is highly desirable in interpreting most blood chemical data, for generally it is the total circulating quantity of nutrient that is important not simply the percentage Urinary excretion tests of various types are available The serum calcium and phosphorus and phosphatase values are almost specific in rickets However, in most instances a definite diagnosis will not be obtained from chemical data alone

Roentgen examination can be of assistance in the diagnosis of rickets scurvy, osteomalacia and osteoporosis The skeletal changes in rickets and scurvy are quite specific Recently roentgenologists have described a so called deficiency pattern in intestinal studies after barium test meals Here again the abnormalities are not specific for nutritional disease but do suggest, none the less, careful consideration of the diet history and the diet in prospective therapy

NITROGEN METABOLISM METHODS

The significance of protein in nutrition warrants a discussion of the fundamental methods in the study of nitrogen metabolism Protein has come to assume a new role in nutrition with the development of knowledge of the more fundamental aspects of the biochemistry of the constituent amino acids In addition to its conventional function as a source of anabolic nitrogen, a source of calories and a delicacy for the palate protein has taken the position of a therapeutic agent, comparable to digitalis or the sulfonamide compounds This development largely of the last two decades has resulted from the observations that certain of the amino acid constituents of dietary protein are essential and have unique roles in metabolism These essential amino acids have much the same position in human food requirements and in diet planning as the vitamins and minerals Much emphasis in investigative work is now placed on these essential nutrients rather than on the food proteins representing the natural mixtures of these substances

With these developments an interesting concept has arisen which is in fact still another application of a generality stated over a hundred years ago by the chemist Justus von Liebig a pioneer in problems of nutrition The generality is known as the 'Law of the Minimum and states that growth and development (Liebig referred to plant requirements) are determined by the availability of that essential substance present in the least amount The problems of protein and amino acid requirements are concerned with the requirements of each of the essential materials present in the diet with their concentrations in the diet and with the effect that diseased states may have on these requirements In practical terms it is of interest to know whether additions to the diet either of protein or of the specific amino acids will favorably influence the course of disease

The most commonly used procedure in the study of nitrogen metabolism both in laboratory animals and human beings has been the measurement of nitrogen balance If one measures the dietary nitrogen intake and the total nitrogen excreted (or lost) in the urine and stools a balance sheet may be made which by difference will represent the gain or loss of nitrogen by the

organism—the values being positive or negative balance respectively An organism is said to be in nitrogen balance when the intake is equal to the output Since the amount of nitrogen in the diet may not be absorbed in entirety, depending on the nature of the protein and the efficiency of the intestinal tract, appropriate corrections must be made in order to calculate the absorbed nitrogen In the normal person the fecal nitrogen is a relatively constant value but will vary with the digestibility of the dietary protein The amino acids obtained *from the diet either as such or as hydrolytic products* are the principal source of body proteins Comparisons of the performance of animals and human beings when receiving various proteins have emphasized the importance of that fraction of the dietary nitrogen which is retained in the body The percentage of absorbed nitrogen that is retained by the body is designated the biologic value of the protein, and it has proved practicable to judge various dietary proteins by this means Allison and Anderson[1] have expressed these relationships as follows

$$B\,V = \frac{AN-(UN-EN)}{AN} \times 100$$

where UN represents *urinary nitrogen*, BV, biologic value AN, absorbed nitrogen and EN is the endogenous nitrogen Endogenous nitrogen represents the *nitrogen which is excreted continuously* as what might be called breakage" nitrogen—the result of essential biochemical procedures which draw on body nitrogen *and result in an irretrievable net loss* Thus on a nitrogen free diet a subject will continue to excrete diminishing amounts of nitrogen

Another useful method for the study of *nitrogen* metabolism has been the measurement of the relationship of depletion or supplementation to measurable variables, for example body weight in the growing *animal* or, somewhat more specifically the measurement of the rate of depletion or regeneration of serum proteins under varying conditions of protein intake Whipple and

[1] Allison J B and Anderson J A The Relation Between Absorbed Nitrogen Nitrogen Balance and Biological Value of Proteins in Adult Dogs *J Nutrition* 29 413 1945

co workers[2] at the University of Rochester have contributed much of the latter evidence These technics offer not only means of comparing the effect of variation of the quality and quantity of nitrogen intake in similar animals but also opportunity to study the response of variable animals under conditions of similar nitrogen intake. The majority of the available evidence in human beings is of the nitrogen balance type

RESPONSE TO THERAPY

Much of the available clinical evidence in the diagnosis of nutritional disease is obtained from supplementation of the diet and study of the patient's response

Dietary manipulations in healthy persons or in persons with chronic nutritional deficiencies are a comparatively simple procedure However diet therapy in acutely ill patients is considerably more difficult, because of anorexia.

A systematic method of procedure in nutritional therapy of diseased patients will simplify considerably the physician's task One may consider that there are three basic levels of intensity of nutritional therapeusis (1) adequate diet (2) supplementary levels of nutrients and (3) therapeutic levels of nutrients Of these an adequate diet is the most fundamental It represents a quantity and selection of food that is available to almost all persons in this country but it can be accomplished in many instances only by direction of food selection and planning of food budgets and supplies In a sick person the aim in therapy must be to encourage a return to maintenance of adequate diet The dietary recommendations of the Food and Nutrition Board of the National Research Council are the most useful standards for this basic diet All physicians should be familiar with these recommendations and know how to obtain them from foods

When the history indicates that an adequate diet cannot be achieved supplementary additions of the essential nutrients are desirable In many instances addition by prescription of special foods of high nutri-

2 Robscheit Robbins, F S Miller L L and Whipple, G H Hemoglobin and Plasma Protein Production—Various Proteins Concentrates, and Digests Influence Blood Protein Production in Anemia and Hypoproteinemia, J Exper Med. 83:463 1946.

tional potency may suffice Thus, addition of citrus fruits, yeast, or liver may accomplish the purpose with the greatest economy If this is impracticable, the addition of low cost, low potency multivitamin preparations may accomplish the same purpose When synthetic vitamin preparations are used for supplementary purposes, they should be added in amounts to approximate the National Research Council's daily recommendations Every attempt should be made to enable the patient to maintain a diet which will accomplish nutritional balance without supplementation Such a diet, skilfully proposed and encouraged, will serve both as a specific therapy in the presence of nutritional disease and as an important application of preventive medicine

Therapeutic levels of vitamin supplementation are indicated in the presence of evidence of one or more specific deficiency diseases Since it is well established that deficiency of a single essential nutrient rarely occurs in human medicine therapy should include supplementation with 5 to 10 times the National Research Council recommendations of the specific nutrient involved with 1 to 5 increments of the remaining Thus a person with pellagra would be treated with 100 to 200 mg of niacin per day with supplementary levels of the remaining vitamin B complex factors This systematized procedure and the composition of the medications has been discussed by Jolliffe[3]

NUTRITIONAL REQUIREMENTS IN DISEASES OF THE GASTROINTESTINAL TRACT

The physician is called on to apply diet therapy most frequently in the management of disorders of the gastrointestinal tract and particularly in disorders of the stomach Peptic ulcer is so prevalent as to be an everyday problem of most practitioners

The treatment of peptic ulcer is designed first to relieve the patient of his symptoms and, second, to attain permanent healing of the ulcer Those patients who do not have a significant degree of obstruction—probably 75 per cent of all patients with ulcer—almost always are well nourished Their appetite digestion and assimilation have not been impaired by the disease There is little evidence to indicate that these patients

3 Jolliffe N The Preventive and Therapeutic Use of Vitamins, J A M A 129 613 (Oct 27) 1945

have been predisposed to their disease by dietary inadequacy or that the course of the disease will be altered by improving the nutritional quality of their diet The eventual success or failure of symptomatic dietary treatment however will to a large extent be based on the degree of cooperation of the patient In this situation the physician must help a patient learn and practice new food habits and hence meet on common ground with the public health nutritionist who attempts to teach entire populations new food habits

The therapy of peptic ulcer is aimed first at relieving symptoms Bland foods such as milk and eggs which are commonly used are fortunately at the same time nutritious The widespread belief that patients with peptic ulcer should be fed a bland soft diet may lead to avoidance of many foods rich in other nutrients, such as vitamins of the B complex vitamin A carotene and various minerals

The 25 per cent of ulcer patients with obstructive lesions pose a more difficult nutritional problem The dietary deficit in this instance is one of calories and protein Aside from the maintenance of water and electrolyte balance in the presence of vomiting and lavage the principal difficulty is one of supplying sufficient calories and protein for maintenance of energy and nitrogen balance until medical treatment leads to subsidence of the obstruction or the obstruction is relieved by surgical methods It is well to remember that in this as in all instances of caloric deficit the prior demand for calories will make other protein and structural requirements of the body subservient Thus in the absence of sufficient calories an otherwise normal supply of protein will be inadequate because of its redirection into energy channels

The frequent use of small nutritious liquid feedings will suffice in mild cases of obstruction Patients requiring parenteral supplementation of caloric intake will likewise require parenteral administration of vitamins However the urgency of caloric requirement will generally force the decision to surgical intervention before a vitamin deficiency becomes of serious consequence

In the present state of knowledge the parenteral use of amino acid compounds seems justified as a prepa

ration for surgical intervention and in patients who respond so slowly to medical treatment that the period of low protein intake and consequent negative nitrogen balance extends over many weeks.

The proposal that frequent oral feedings with protein hydrolysate and a commercial carbohydrate preparation[4] is an advance in diet therapy of peptic ulcer has not been confirmed. It seems unlikely that this form of diet has advantages over more economical and equally nutritious foods in general use. There is evidence that, contrary to theoretical expectations, the buffering action of the amino acids and polypeptides may be offset by an apparent stimulation of the acid-secreting cells of the gastric mucosa.[5]

The internist is often responsible for the care of patients after surgical treatment for ulcer. Several careful reports[6] have indicated that, although patients who have undergone gastrectomy are generally able to maintain their weight—and few of them develop the pernicious anemia anticipated—many of them (up to 25 per cent) according to Zollinger and Hoerr[7] exhibit postprandial symptoms of serious consequence. The symptoms have been given the expressive but inaccurate name of "the dumping syndrome." In many patients two distinct phases of the syndrome follow meals. The first is believed due to rapid and extensive filling of the jejunum and the second is believed to be consequent to a hypoglycemic period following the initial rapid absorption of carbohydrates. These symptoms may be controlled effectively by assuring that the patient procure not less than 50 per cent and preferably more of his total caloric requirement from protein and fat, thus reducing the intake of rapidly absorbable carbohydrate, which seems to be one immediate cause of the symptoms.

4. Co Tui, Wright, A. M., Mulholland, J. H., Galvin, T., Barcham, I., and Gerst, G. R.: Hyperalimentation Treatment of Peptic Ulcer with Amino Acids (Protein Hydrolysates) and Dextri-Maltose, Gastroenterology 5: 5, 1945.

5. Hodges, H. H.: Protein Hydrolysate Therapy for Peptic Ulcer, Gastroenterology 8: [illegible], 1947.

6. Custer, M. D., Jr., Butt, H. R., and Waugh, J. M.: The So-Called "Dumping Syndrome" After Subtotal Gastrectomy, Ann. Surg. 123: [illegible], 1946.

7. Zollinger, R. M., and Hoerr, S. O.: Gastric Operations, Troublesome Postoperative Symptoms with Special Reference to Carbohydrate Ingestion, J. A. M. A. 134: 575 (June [illegible]) 1947.

That only a small number of patients with total gastrectomies have required treatment for pernicious anemia has been surprising. Patients subjected to this procedure should be carefully observed, however, since this complication may produce irreparable damage to the nervous system before treatment is begun.

In attempts to relieve the pain of peptic ulcer almost every patient is given an antacid medication of some sort. That this procedure may do more than reduce gastric acidity and alleviate symptoms for a few hours is indicated by the finding of Robinson and his co-workers[8] that certain antacids as magnesium trisilicate act as efficient adsorbers of thiamine, thus making dietary thiamine partially unavailable. Although it is well known that several of the B complex vitamins are unstable in vitro when exposed to alkaline solutions, there is little evidence that the brief encounter of the vitamins with antacids in the stomach will lead to a serious impairment of available vitamins.

Probably the most frequent contributing cause in nutritional deficiency is diarrhea. Irrespective of the nature of the diet, if the passage of food through the gastrointestinal tract is so rapid that absorption is limited, poor nutrition will result. In addition, diarrhea often characterizes diseases in which the absorptive capacity of the mucosal surfaces has been impaired. When infections occur along the tract, hypermotility appears, anatomic changes slow the absorptive process, and the systemic reactions to the infection may increase requirements. These factors working concertedly lead to malnutrition and, in a vicious cycle, to acute deficiency states. There is, in addition, the uncertain effect these circumstances may have on the intestinal flora and its natural supply of essential nutrients. Aside from the use of diet as *symptomatic treatment*, the greatest importance to the outcome of the disease will attend the degree to which requirements for essential nutrients, including proteins and calories, are met. Severe diarrhea more than any other medical problem demands complete parenteral nutrition. This is at present impossible because of lack of means of supplying sufficient calories.

8 Robinson, W. D., Melnick, D., and Field, H., Jr. Urinary Excretion of Thiamine in Clinical Cases and the Value of Such Analysis in the Diagnosis of Thiamine Deficiency. J. Clin. Investigation 19: 339, 1940.

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Probably the most frequent contributing cause in nutritional deficiency is diarrhea. Irrespective of the nature of the diet if the passage of food through the gastrointestinal tract is so rapid that absorption is limited poor nutrition will result. In addition, diarrhea often characterizes diseases in which the absorptive capacity of the mucosal surfaces has been impaired. When infections occur along the tract hypermotility appears anatomic changes slow the absorptive process and the systemic reactions to the infection may increase requirements. These factors working concertedly lead to malnutrition and in a vicious cycle to acute deficiency states. There is in addition the uncertain effect these circumstances may have on the intestinal flora and its natural supply of essential nutrients. Aside from the use of diet as symptomatic treatment, the greatest importance to the outcome of the disease will attend the degree to which requirements for essential nutrients including proteins and calories are met. Severe diarrhea more than any other medical problem demands complete parenteral nutrition. This is at present impossible because of lack of means of supplying sufficient calories.

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Considerable information has been obtained concerning the means of meeting water and electrolyte requirements.[9] The most crucial problem in the treatment of acute diarrhea is that of supplying the energy deficit. Glucose solutions are limited by their low calorie concentration when considered in terms of hypertonicity and fluid volume. Protein digests will supply nitrogen requirements but, unless energy requirements have been supplied, they will be unceremoniously burned for calories and the need for anabolic nitrogen will persist.

Chung and Viscorova[10] have recently advocated a program of forced feeding (orally) in diarrhea of infants rather than fasting as has been the custom. This procedure has the advantage that such restricted absorption as remains will be used to the fullest extent. Clinical evaluation of this procedure suggests favorable results.

Parenteral supplementation with the water soluble vitamins is indicated with persistent diarrhea. Preparations of vitamins A and D for parenteral use are now becoming available and should be used. The water and electrolyte balance may be maintained with parenterally administered mixtures. Darrow[11] has recently pointed out the need for potassium replacement in diarrhea of infants. Whether this occurs also in adults with severe diarrhea is not established. Until a suitable concentrated source of calories for parenteral use, such as an emulsion of fat, is developed the attempt to supply calories must be for the most part by the oral route. There is little if any evidence to support the contention that hydrolyzed proteins in the form of amino acid polypeptide mixtures have any advantage over natural protein as a source of dietary nitrogen or calories in diarrhea. In addition they are not palatable and are considerably more expensive.

The notable exception to this criticism of protein hydrolysates is in the dietary treatment of absorptive disorders due to a specific deficiency of proteolytic

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9. Franklin, W. Z. General Treatment of Diarrheal Diseases, Am. J. Digest. Dis. 2: 263, 1945.

10. Chung, A. W., and Viscorova, P. The Effect of Early Oral Feeding Versus Early Oral Starvation as the Cause of Infantile Diarrhea, J. Pediatrics 33: 14, 1948.

11. Darrow, D. C. Advances in the Treatment of Diarrhea in Infants, Texas Rep. Biol. & Med. 5: 29, 1947.

enzymes as in pancreatic disease.[12] In this instance the oral use of amino acids is probably more satisfactory than an attempt to supplement the deficient proteolytic enzymes by orally administered enteric coated enzyme preparations.

It has been suggested by several authors that the use of certain highly active adsorbing agents as kaolin or fuller's earth in the symptomatic treatment of diarrhea may not be desirable since these compounds have been shown to adsorb and thus make unavailable dietary thiamine and perhaps other essential dietary constituents.[13] These adsorbing agents have long been used by biochemists to concentrate natural sources of B complex vitamins. Until thiamine was synthesized a fuller's earth adsorbate of a rice polish extract was for a time the international standard of thiamine. This standard was abandoned when it was shown that the rat could utilize only 50 per cent of the adsorbed vitamin.

The initial discovery that in monkeys maintained on a diet deficient in a factor called vitamin M, later shown to be folic or pteroylglutamic acid, diarrhea developed in addition to pancytopenia has now assumed clinical importance. The similarity of the "sprue syndrome" in man led Darby and Jones[14] to test pteroylglutamic acid as a therapeutic agent in human beings. Previous experience in many clinics had confirmed the suggestion that the anemia of sprue was often responsive to liver extracts given parenterally. Darby found that 15 mg. of synthetic pteroylglutamic acid given intramuscularly daily relieved the symptoms within two weeks and improved the hematologic deficiency. Spies[15] has confirmed these observations.

It may be inferred, then, that sprue is a specific deficiency disease since it appears to be cured by pteroylglutamic acid. The etiology is confused, however, and the relationship of these observations to the epi

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12. Homburger, F.: Use of Protein Hydrolysates by Mouth. Am. J. Med. 3:430, 1947.

13. Melnick, D., Hochberg, M., and Oser, B. L.: Physiological Availability of the Vitamins. VI. The Effect of Adsorbents on Thiamine. J. Nutrition 30:233, 1945.

14. Darby, W. J., and Jones, E.: Treatment of Sprue with Synthetic L. Casei Factor (Folic Acid, Vitamin M). Proc. Soc. Exper. Biol. & Med. 60:259, 1945.

15. Spies, T. D.: Effect of Folic Acid on Persons with Macrocytic Anemia in Relapse. J. A. M. A. 130:474 (Feb. 23) 1946.

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demiology of sprue is not clear If the absorptive defect can be corrected by abolishing the diarrhea, the serious disorders of calcium metabolism hypoprothrombinemia, hypotocopherolemia and multiple water-soluble vitamin deficiencies are no longer a problem

The past ten years have produced remarkable advances in our knowledge of the treatment for pernicious anemia The development of pteroylglutamic acid (folic acid) led to a water-soluble vitamin which at least partially treats the hematologic defect in pernicious anemia It has been repeatedly shown, however, that folic acid therapy will not prevent progression of the neurologic components of pernicious anemia[16] Within the past year a new member of the water soluble vitamin complex, vitamin B_{12}, has been announced[17] Preliminary trials indicate that this vitamin given parenterally will produce effective remissions of all the manifestations of pernicious anemia[18] Other clinical trials of this material have indicated[19] that vitamin B_{12} appears to be identical with the antipernicious anemia principle of liver One unit of liver activity is approximately equivalent to 1 microgram of vitamin B_{1} Observations by Berk and his co-workers[19] show that vitamin B_{12} administered orally to patients with pernicious anemia has little if any hematopoietic activity Simultaneous administration of normal gastric juice with orally administered vitamin B_{12} produced a hematopoietic response This evidence suggests the presence of an intrinsic factor necessary for the utilization of dietary sources of the 'extrinsic" factor which is presumably vitamin B_{12}

The nutritional failure of patients with ulcerative colitis is characteristic of this disease Welsh and his co-workers[20] have shown in studies on a few patients that the most pressing nutritional need was for protein

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16 Ross J F Belding H and Paegel B L Development and Progression of Subacute Combined Degeneration of Spinal Cord in Patients with Pernicious Anemia Treated with Folic Acid Blood **3** 68 1948

17 Rickes E L Brink N G Koniuszy F R Wood T R and Folkers K Crystalline Vitamin B_{12}, Science **107**:346 1948

18 West R Activity of Vitamin B_{12} in Addison an Pernicious Anemia Science **107** 348 1948

19 Berk L Castle W B Welch A D Heinle R W Anker R and Epstein M Observations on the Etiological Relationship of Achylia Gastrica to Pernicious Anemia X Activity of Vitamin B_{12} as Food (Extrinsic) Factor New England J Med **239**:911 1948

20 Welsh C S Adams M and Wakefield E G Metabolic Studies on Chronic Ulcerative Colitis J Clin Investigation **16**:161 1937

They found that the fecal nitrogen loss became the major pathway of nitrogen excretion and that this loss of nitrogen was proportional to other signs of activity of the disease. They believe that exudation and tissue destruction with continuing hemorrhage are the principal causes of the negative nitrogen balance—and not the hypermotility of the small intestine with poor absorption as is generally supposed. Other investigators[21] have shown that patients with colitis show abnormally low serum levels for almost every vitamin that can be measured. Caloric deficiency is undoubtedly of equal importance to protein deficiency in ulcerative colitis.

The diet therapy must be inclusive. Ideally the *maximum degree of nutrition both quantitatively and qualitatively* is sought with the least possible amount of mechanical irritation of the colon. Since most of these patients have anorexia and are well aware that eating often precipitates a new bout of diarrhea, the task is not simple. In so far as the oral nutrition falls short of conservative estimates of daily requirements of vitamins, proteins, and calories, parenteral supplementation should be used. Here again the attainment of caloric balance is almost impossible with present procedures, and this failure will often confound the best attempts to correct a mounting nitrogen deficit.

A discussion of nutrition and diseases of the intestinal tract should include at least a comment on the use of liquid petrolatum, a commonly used gastrointestinal medicament. Experimental nutritionists have known for many years that inclusion of hydrocarbon oils ("mineral oil") in animal diets may lead to fat soluble vitamin deficiencies.[22] Javert and Macri[23] pointed out the potentially *serious consequences of the use of liquid petrolatum* for laxation during pregnancy through the consequent lowering of the prothrombin level, presumably a manifestation of vitamin K deficiency. This effect is produced by the preferential solubility of the fat soluble vitamins

21 Bercovitz, Z., and Page, R. C.: Metabolic and Vitamin Studies in Chronic Ulcerative Colitis, Ann. Int. Med. 20: 39 and 254, 1944. Mackie, T. T., Eddy, W. H., and Mills, M. A.: Vitamin Deficiencies in Gastro-Intestinal Disease, Ann. Int. Med. 14: 8, 1940.

22 Burrows, M. T., and Farr, W. K.: The Action of Mineral Oil per Os on the Organism, Proc. Soc. Exper. Biol. & Med. 24: 719, 1927. Mineral Oil in Foods: Report of the Council on Foods, J. A. M. A. 123: *967 (Dec. 6) 1943.*

23 Javert, C. T., and Macri, C.: Prothrombin Concentrations and Mineral Oil, Am. J. Obst. & Gynec. 42: 409, 1941.

in the largely unabsorbable oil There is, in addition, evidence [24] that, if liquid petrolatum is sufficiently subdivided in the intestinal emulsion, it may be absorbed The *absorption of liquid petrolatum leads in experi*mental animals and human beings to demonstrable depositions of the material in the mesenteric lymph nodes and the liver Typical foreign body reactions occur about these sites [25] A recent report by Mahle and Patton [26] summarizes the available evidence pertinent to this problem The use of hydrocarbon oils for laxation does not seem to be a sound procedure.

NUTRITION IN HEPATIC DISEASE

The magnitude of the enthusiasm in clinical circles supporting dietary treatment of acute and chronic disease of the liver justifies some reexamination of the pertinent evidence

The etiology of cirrhosis of the liver, a common medical problem remains obscure The hypothesis that this chronic disease of the liver in man is caused by a nutritional deficiency has not been proved, however, a disease has been produced in several species of animals by dietary restrictions which simulates human cirrhosis in most respects There are many reports in the medical literature concerning the effectiveness of a variety of diet therapies and the use of one or several nutritionally essential factors as separate supplements in the treatment of hepatic disease in human beings The conclusions of these investigations are in disagreement Whatever the outcome of these researches the clinician will do well to remain a pragmatist Common experience indicates that cirrhotic patients often get along well when treated with nutritionally adequate diets alone

The concept that ethyl alcohol alone acts as a toxin to damage liver cells and that its use leads to cirrhosis has not been confirmed In experimental animals alcohol seems to act synergistically with other mechan

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24 Frazer A C Stewart H C and Schulman J H Emulsification and Absorpt on of Fats and Paraff ns in the Intest ne Nature **149:** *167* 1942

25 Stryker W A Absorption of L qui l Petrolatum (Mineral Oil) from Intestine Hist log c and Chem cal Study Arch Path. **31:** 6/0 (June) 1941

26 Mahle A E and Patton H M Carotene and V tam n A Metabolism in Man Th ir Ex etion and Plasma Lev l a Influ nced by Orally Administered Mineral Oil and a Hyd oph l c Mucilloid Gastroenterology **9:** 44 1947

isms to produce cirrhosis but alone does not. The dietary inadequacy which follows in the wake of alcoholism taken with the high incidence of cirrhosis in populations that subsist on marginal diets suggests that this is in part, a deficiency disease.

The belief that a high carbohydrate diet protects the liver from subsequent injury stems from the work of Rosenfeld[27] and Opie and Alford.[28] More recent work has indicated that the protein in the diet and available to the liver at the time of damage is of considerably more importance. The significance of the protein stores in preventing liver damage is continually emphasized in animal work and has received some clinical affirmation.

An additional complexity has been the evaluation of the place of lipotropic agents in the treatment of hepatic disease. Of these choline methionine and inositol have received attention. A dietary deficiency of choline will lead to a fatty liver in the rat and dog. Several clinical reports have indicated favorable results from the treatment of Laennec's cirrhosis with 10 to 50 Gm of choline chloride daily.[29]

High carbohydrate diets or the parenteral use of carbohydrate in the treatment of a damaged liver or in anticipation of liver damage as before anesthesia is based on the belief that as liver glycogen is laid down liver cell lipids will be removed. Ravdin and his co-workers[30] pointed out that adequate protein sources and sufficient carbohydrate to spare this protein from energy consumption is the important aspect of this apparent lipotropism of carbohydrate.

The importance of protein in protection of the liver against injury has been confirmed by many workers.[31] Methionine an essential amino acid and proteins rich

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27 Rosenfeld G Fettbildung Ergebn. d Physiol. 2:50 1903

28 Opie, E L., and Alford L. B The Influence of Diet on Hepatic Necrosis and Toxicity of Chloroform. J A. M A 6?:895 (March 21) 1914

29 Russakoff A. H and Blumberg H Choline as Adjuvant to Dietary Therapy in Cirrhosis of the Liver Ann Int. Med. 21:848 1944 Beams, A. J Cirrhosis of the Liver J A. M A 130:190 (Jan 6) 1946

30 Ravdin I S and others Prevention of Liver Damage and Facilitation of Repair in Liver by Diet J A. M A. 121:3 2 (Jan 30) 1943

31 Goldschmidt S Vars H M and Ravdin I S The Influence of the Foodstuff Upon the Susceptibility of the Liver to Injury by Chloroform and the Probable Mechanism of Their Action J Clin Investigation 18:277 1939 Miller L. L. Ross J F and Whipple, G H Methionine and Cystine Specific Protein Factors Preventing Chloroform Liver Injury in Protein Depleted Dogs Am J Med Sc. 200:739 1940

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24 Frazer A C Stewart H C and Schulman J H Emulsification and Absorption of Fats and Paraffins in the Intestine, Nature **149** 167 1942

25 Stryker W A Absorption of Liquid Petrolatum (Mineral Oil) from Intestine Histologic and Chemical Study Arch Path. **31** 670 (June) 1941

26 Mahle A E and Patton H M Carotene and Vitamin A Metabolism in Man Their Excretion and Plasma Level as Influenced by Orally Administered Mineral Oil and a Hydrophilic Mucilloid Gastroenterology **9** 44 1947

tious hepatitis demands thorough diet education of the patient with continuation of optimal protein and vitamin intake for many months.

The concept of the value of a low fat diet in the therapy of hepatic disease which rested practically on the observed intolerance of fat of some patients with hepatic disease and theoretically on the poorly founded belief that fat in itself when present in the liver was deleterious has been challenged by several reports Hoagland and others[33] found that convalescence from hepatitis was in fact shortened by liberal fat intake in the diet, presumably by reason of the improved palatability and thus better consumption of the high protein high vitamin diet used

NUTRITIONAL NEEDS IN RENAL DISEASE

With the exception of the treatment for infection and some neoplastic and traumatic disorders the therapy of renal disease is nonspecific and largely symptomatic The concepts behind most of the commonly used diet therapy methods are of ancient origin Fishberg[34] states, The regulation of the diet forms the corner stone of the treatment of glomerulonephritis '

One of the fundamental tenets has been that since protein metabolism calls on renal excretion of end products and since fat and carbohydrate are burned to water and carbon dioxide which may be disposed of extrarenally protein should be limited in the diet of patients with impaired renal function in order to afford physiologic rest Since the elevation of serum non protein nitrogen is an easily measured index of renal functional impairment it has been considered prime evidence of the relationship in nitrogenous intake impaired excretory function and uremia It is in fact frequently observed that the amount of nitrogen in the diet will influence the level of the serum nonprotein nitrogen and recently Addis and his co workers[35]

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33 Hoagland, C. L. Therapy of Liver Disease Bull New York Acad Med 21:537 1945 Wilson C Pollock M R. and Harris A D Diet in the Treatment of Infective Hepatitis Therapeutic Trial of Cystine and Variation of Fat Content Lancet 250:881 1946

34 Fishberg A M Hypertension and Nephritis ed 4 Philadelphia, Lea & Febiger 1944 p 481

35 Addis T Barrett E Poo L J and Yuen D W Relation Between Serum Urea Concentration and Protein Consumption of Normal Individuals J Clin. Investigation 26:869 1947

in this amino acid act as does choline in mobilizing liver lipids Both choline and methionine, the common attribute of which is believed to be the presence of a labile methyl group, act to protect the liver in dogs maintained on low protein diets when chloroform is given as a poison Although inositol, an isomer of glucose, has been shown to exhibit lipotropic properties under certain conditions in laboratory animals, there is no evidence to support the use of inositol in the treatment of hepatic disease in human beings The crucial question which remains, however, is whether these substances, which are effective when given experimentally preparatory to liver damage, are also of value clinically when administered following the liver damage Many clinicians assume that this is true and advocate not only high protein (100 to 150 Gm per day) diets but supplementation with choline and/or methionine given orally We believe that this remains an open question

Since the liver is known to be intimately concerned with the metabolism and storage of many of the vitamins, it would be expected that in a chronic progressive disease such as cirrhosis, in which the effective functional liver tissue is steadily diminished multiple vitamin deficiencies would result Deficiencies of both vitamins A and D have been found, frequently requiring supplementary therapy Vitamin K therapy parenterally will support the prothrombin level until liver failure becomes marked Therapy with supplementary levels and preferably with natural sources, as dried yeast, provided this is given in adequate amounts (40 to 50 Gm daily) supplies B complex vitamins and, in addition contributes protein [32]

Similar considerations apply to hepatitis of virus origin The characteristic anorexia and nausea of the early clinical stages of the disease present serious problems Parenteral nutrition with protein hydrolysates and glucose is often necessary The vitamin requirements in infectious hepatitis are not known to be altered Supplementary dosages of vitamins are probably desirable as a precautionary measure The tendency to chronicity with occasional relapse of infec

32 Patek A J Jr and Post J Treatment of Cirrhosis of the Liver by a Nutritious Diet and Supplements Rich in Vitamin B Complex J Clin Investigation 20 481 1941

are applicable to the diets of these patients Aside from a variable content of fixed base as sodium which may be of importance to patients with water retention or edema, there are no known protein constituents harmful to patients with nephritis.

The observation that animals will develop vascular and renal lesions after large amounts of dietary protein has been confirmed by several laboratories[40] Knowledge of these phenomena in human beings is lacking

The problem for the clinician then, is one of diet regulation which will least retard and most stimulate the remarkable ability of the kidneys to restore damaged function Except in acute renal emergencies characterized by lack of urine excretion usually of short duration the protein intake should be sufficient to maintain nitrogen balance In a patient at rest without fever this may be as little as 30 to 40 Gm per day However since appetite is often poor and the caloric requirement satisfied with difficulty there would seem to be few occasions when less than 1 Gm of protein per day per kilogram of body weight should be given In the presence of significant proteinuria the dietary protein intake should be supplemented with an amount of protein equivalent in grams to that lost in the urine Restriction of salt and selection of protein sources of low salt content are indicated in the presence of edema or salt retention When the appetite and salt tolerance will allow the use of dietary protein as a source of urea and anions as stimulants to diuresis may sometimes be useful However administration of urea and ammonium chloride is generally more effective

The dietary management of edema occurring with nephritis has recently been discussed by Thorn and Tyler[41] The limitation of the sodium intake is of prime importance The inability of the diseased kidney to excrete the sodium ion is the basis of most "renal" edema. Since much of the sodium (as sodium chloride) in food is added during the preparation or at the table restriction of these practices will decrease the salt intake to less than 5 Gm per day A daily salt intake of less

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40 Newburgh L. H The Production of Bright s Disease by Feeding High Protein Diets Arch. Int Med. 24:359 (Oct) 1919 Nuzum F R, Segal, B Garland R and Osborne M: Arteriosclerosis and Increased Blood Pressure Experimental Production Arch Int. Med 37:733 (June) 1926

41 Thorn, G W, and Tyler F H: Clinical Management of Edema in Bright s Disease, M Clin. North America 31:1077 (Sept.) 1947

have shown that in healthy adults the level of blood urea nitrogen is influenced by the amount of nitrogen in the diet

Admittedly, nitrogen excretion is only one of many functions of the kidney It may be questioned then whether the amount of physiologic 'rest" and 'symp tomatic" treatment of the nitrogen retention which one obtains by diet restriction of protein is significant or beneficial There is no evidence that a liberal allow ance of protein i e 60 to 80 Gm per day is harmful even in the presence of azotemia There are many who question the restriction of diet protein in the presence of renal disease The part that this restriction coupled with loss of protein through the urine plays in the development of asthenia anemia hypoproteinemia and edema may be greater than is realized[36] Also pertinent to the dietary treatment of diseases of the kidney is the evidence that high protein diets lead to higher urea clearance values in normal experimental dogs as com pared with dogs on low protein diets, and similarly the renal blood flow is increased by a high protein diet[37]

There are other experimental observations which may be of importance in this problem The discovery by Masugi[38] that a form of glomerulonephritis simulating the human variety could be produced in rats by the injection of 'anti rat kidney" rabbit serum led Farr and Smadel[39] to investigate the effect of diet on the course of this experimental nephritis It was found that high protein diets led to a higher mortality among the diseased rats

The ancient belief common still among the laity, that red meats are more harmful than white meats to patients with renal disease has no basis in fact Neither is there reason to believe that plant proteins are more beneficial than animal proteins or vice versa The same prin ciples of nutritive value based on the biologic value

36 Weiss S Diet and Bright s Disease Conn. State Med J 5 496 1941

37 Jolliffe N and Sm th H W The Exc etion of Urine in the Dog II The Urea and Creatin ne Clearance on Cracker Meal D et Am J Physiol. 99: 101 1931 Van Slyke D D Rhoads C P Hiller A and Alving A. The Relationsh p of the Urea Clearance to the Renal Blood Flow Am J Phys ol 110: 387 1934

38 Masugi M Ueber die Experimentelle Glomerulonephrit s durch das spezifische Antinierenserum Be tr path Anat. u allg Path 92: 429 1933

39 Farr I E and Smadel, J F Influence of D et on the Course of Nephrotoxic Neph itis in Rats Proc. Soc. Exper Biol & Med. 36: 472 1937

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40 Newburgh L. H The Production of Bright's Disease by Feeding High Protein Diets, Arch. Int. Med. 24:359 (Oct) 1919 Nuzum F R. Seegal, B Garland R., and Osborne M Arteriosclerosis and Increased Blood Pressure Experimental Production Arch. Int. Med. 37:733 (June) 19 6

41 Thorn G W, and Tyler F H Clinical Management of Edema in Bright's Disease, M. Clin. North America 31:1077 (Sept.) 1947

than 1 Gm per day (often required) will necessitate elimination of all added salt and avoidance of salted foods including bread, butter and bakery products Such a diet will often require vitamin supplementation, since the natural vitamin content of the diet may be low, especially in riboflavin

Acid ash diets may be of assistance in augmenting diuresis The net ash of the diet is effective in diuresis because residual metabolic anions must be excreted in combination with fixed base Thus an acid ash diet acts to encourage the kidney to eliminate sodium and allow water to be lost If the sodium intake is adequately controlled there is no real reason to restrict the water intake since the water retained will be determined by the salt retained The usefulness of water itself as a diuretic agent has been reemphasized by Schemm [42] who advocates a low sodium high fluid intake for patients with edema

Because of their unpalatability, high salt content and lack of evidence that hydrolyzed proteins possess any advantages over native proteins, oral therapy with these materials is of questionable value. In addition, they are considerably more expensive Parenteral amino acid therapy is occasionally used as an emergency means of supplementing a deficient oral intake of protein but, unless caloric intake is adequate much of the parenterally administered protein will simply serve as an expensive source of calories The use of whole blood or plasma or derived plasma proteins to raise levels of serum protein remains an experimental and as yet impractical solution to the problem of hypoproteinemia of renal disease Although the mechanism is unknown there would seem to be an unrecognized metabolic defect in the patient with nephritis which prevents active or efficient reconstruction of plasma proteins Until this problem is better understood, dietary therapy of the hypoproteinemia of nephritic patients is distressingly ineffective

There is no evidence of specifically increased requirements of the vitamins or minerals in renal disease except possibly in salt-losing nephritic patients and in the potassium deficiency occurring after massive

42 Schemm F R A High Fluid Intake in the Management of Edema, Especially Cardiac Edema I The Details and Basis of the Regime Ann Int. Med **17** 952, 1942 II Clinical Observations and Data ibid. **21** 937 1944

diuresis. The human counterpart of acute hemorrhagic nephritis[43] seen in young rats maintained on choline deficient diets has not been observed

NUTRITIONAL NEEDS IN UROLITHIASIS

Diet therapy is an important adjunct to the surgical treatment of urolithiasis. There is good experimental evidence that inadequate diets may lead to calculi formation in the urinary tract of animals[44] and suggestive epidemiologic evidence that the prevalence of urolithiasis in the Orient for example, is directly related to the diet of the population affected The value of dietary regulation lies in the prevention and the arrest of growth of stones. Diet therapy will rarely dissolve formed stones Laboratory evidence indicates that strongly acid urine in the presence of high urinary purine excretion favors formation of uric acid and urate stones Reduction of purine rich foods and maintenance of neutral or alkaline urine by dietary methods is indicated when the stones are of purine origin

Calcium-containing stones are primarily influenced by the amount of calcium excreted through the urine and the p_H of the urine Hypercalciuria may be the result of dietary manipulation but is not usually caused by this More significant causes of hypercalciuria are metabolic disorders such as hyperparathyroidism or the calcium mobilization consequent to bedrest The chemical composition of the calcium containing stones is largely determined by the reaction of the urine. Diet management should include insurance of adequate and balanced amounts of calcium and phosphorus Oxalate intake should be reduced since calcium oxalate stones are common. When the hypercalciuria is of metabolic origin maintenance of large volumes of neutral urine is of prophylactic value until the defect in calcium metabolism can be corrected Calcium phosphate stones occurring in alkaline urine are a particular complication of hyperparathyroidism The importance of maintaining an acid reaction in the urine is great The same precaution pertains to the care

43 Griffith W H and Wade N J Choline Metabolism I. The Occurrence and Prevention of Hemorrhagic Degeneration in Young Rats on a Low Choline Diet J Biol. Chem 131:567 1939

44 Hammarsten G Dietetic Therapy in the Formation of Calcium Oxalate Calculi in the Urinary Passages II Skandinav Arch. f Physiol. 80:165 1938

of patients with prolonged immobilization when the atrophy of disuse allows large amounts of skeletal calcium to be excreted in the urine The prolonged adherence to an alkalinizing regimen, as in the treatment of peptic ulcer, predisposes to calcium phosphate stones [45]

The importance of vitamin A deficiency in initiating epithelial defects which lead to stone formation is still debated An adequate allowance of vitamin A or carotene in the daily diet should be insured The importance of nutrition in the etiology of urolithiasis is well summarized by Lowsley and Kirwin [46] as follows

> That lithiasis is a deficiency disease is borne out by the notably decreased incidence of urinary stone—particularly bladder stone—in civilized countries in childhood since the institution of modern diets which prevent avitaminosis Fresh vegetables milk and cod liver oil have probably contributed more than any other factors to this lessening of the incidence of urinary stone in childhood

NUTRITIONAL NEEDS IN CARDIOVASCULAR DISEASE

Diseases of the vascular system with their ramifications constitute a common medical problem for the physician and because of their frequency and devastating course now represent the greatest single menace to the health of the general population Both the knowledge of etiology and treatment of these diseases remain unsatisfactory

The widespread occurrence and slowly progressive course of vascular sclerosis the most fundamental of cardiovascular diseases suggest the presence of a similarly widespread and continuing environmental factor which may be in part responsible for this disease Diet is undoubtedly the single most important environmental factor in present day civilization in this country and deserves thorough study in relation to this disease

Experimental work has been done in animals which seems to incriminate the cholesterol moiety of the diet as a responsible factor in vascular sclerosis [47] The

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45 Eisele C W Role of Alkali Therapy for Peptic Ulcer in Formation of Urinary Calculi J A M A 114:2363 (June 15) 1940
46 Lowsley O S, and Kirwin T J Clinical Urology ed 2 Baltimore Williams & Wilkins 1944 vol 2 p 1589
47 Leary T Arteriosclerosis Bull New York Acad. Med 17:887 1941.

earlier work with cholesterol was done with rabbits and chickens and may be criticized in that the atherosclerosis produced was in herbivorous species which normally do not ingest cholesterol and have insufficient biochemical mechanisms for its disposal. More recently similar observations have been made in dogs which were also fed thiouracil.[48]

Selye and Stone[49] have described vascular lesions produced in several species by the concomitant conditions of a high protein, high sodium chloride diet and injections of large amounts of *desoxycorticosterone* acetate. Selye calls the associated physiologic adaptive reactions the "alarm reaction." Investigation of this response may illuminate the entire problem of vascular sclerosis.

The restriction of protein intake in patients with hypertension is an ancient practice. Even in the presence of demonstrable renal damage stringent protein restriction with the intent of lowering the serum nonprotein nitrogen is not justifiable. There would seem to be no complication of cardiovascular disease aside from the brief cardiac emergency states requiring less than the normal allotment of 60 to 70 Gm. of protein per day. Neither is there evidence to indicate that excessive *amounts of protein are of value*. The belief that the high specific dynamic action of protein leads to excessive demands on the heart is of no practical importance. Of greater significance may be the observations that administration of ammonium salts commonly used as diuretics in cardiac disease causes a large increase in heat production and consequently in cardiac work.[50]

The *management of cardiac edema by restriction of* salt as outlined by Allen and Sherrill[51] is theoretically and in practice similar to the management of the edema of nephritis previously discussed.

The use of restricted salt diets is often advisable in cardiac disease as a prophylactic measure. Despite the small hardship it may work on the patient, the physician

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48 Steiner, A., and Kendall, F. E.: Atherosclerosis and Arteriosclerosis in Dogs Following Ingestion of Cholesterol and Thiouracil, Arch. Path. 42:433 (Oct.) 1946.

49 Selye, H., and Stone, H.: Pathogenesis of the Cardiac and Renal Changes Which Usually Accompany Malignant Hypertension, J. Urol. 56:399, 1946.

50 Lundsgaard, E.: Ueber die Ursachen der Spezifischen Dynamischen Wirkung der Nahrungsstoffe, Skandinav. Arch. f. Physiol. 62:243, 1931.

51 Allen, F. M., and Sherrill, J. W.: Treatment of Arterial Hypertension, J. Metabolic Research 2:429, 1922.

is often able to anticipate the development of congestive failure or peripheral edema and delay these misfortunes by means of low salt diets Again, in anticipation of congestive failure when visceral edema impairs utiliza tion, supplementary levels of vitamins are indicated

Management of the caloric balance in cardiovascular disease is of extreme importance It is well established that blood pressure increases with obesity [52] and con versely, that hypertension is a common complication of obesity [53]

The rational practical concept of obesity so well summarized by Newburgh and Conn [54] is worth the careful consideration of every physician Obesity in any circumstance represents the end result of a period of positive energy balance Correction of obesity is achieved by reversal of this balance whether by reduc tion in energy input or increase in energy output Cor rection of biochemical lesions (resulting from endocrine disorders, for example) which influence the over all energy exchange are correlative procedures The devastation which obesity produces as reflected in life expectancy statistics is well established More than any other group of diseases cardiovascular disease is augmented by the complication of obesity for not only is the work of the heart increased by the mechanical load but evidence is pointing to biochemical factors which encourage vascular disease in obesity

A recent development in the treatment of obesity has been the introduction of the dextrorotatory isomer of amphetamine It had previously been observed that *l* amphetamine sulfate when given orally led to a diminution of appetite and loss of weight The *d* amphetamine sulfate is reputed to be more effective and less toxic Gelvin and McGavack [55] studied this drug as an adjunct to therapy of obesity and found that, although an initial weight reduction could be effected the weight loss was temporary and a plateau would soon be reached Further study is needed but

52 Symond B The Blood Pr ssu e of Healthy Men and Women, J A M A **80** 23, (Jan 27) 1923

53 Terry A H Jr Obe ty and Hypertension J A M A **81** 1283 (Oct 13) 1923

54 Newburgh L H Obe ty I En rgy Metabolism Physiol Rev **24** 18 1944 Conn J W Obes ty Et olog cal Aspects Physiol Rev **24** 31 1944

55 Gelvin E P and McGava k T H Dexedrine and Weight Reduction, New York State Med J **49**: 279 1949

at present it seems most probable that reduction of weight will depend on restriction of voluntary intake by more overt means.

Although some evidence has been obtained indicating usefulness of B complex vitamins in the treatment of myocardial infarction,[56] this therapy is not established. The use of the Karell diet (nothing but 800 cc of milk per day) in the emergency phases of congestive failure is based on practicality. This diet is an interesting example of an empiric choice designed to accomplish limitation of calories and salt with palatability. This milk diet should not be continued for more than a few days unless supplemented with iron thiamine niacin and ascorbic acid and larger quantities of milk are used. The sodium content of milk is 0.047 Gm per hundred milliliters. When the patient's appetite returns a more adequate diet may be planned with restriction of salt and calories as necessary and with more liberal water and vitamin content.

A recent dietary treatment of hypertension which has received considerable acclaim is the "rice diet."[57] It is well to point out that this diet is nutritionally inadequate, particularly with respect to protein and vitamin content. The unpalatability of the diet often leads to caloric deficiency. We are inclined to believe that such efficacy of the diet in reducing blood pressure as is observed is primarily due to the low salt content coupled with a caloric deficit and consequent weight reduction. Master and his co-workers[58] have described the salutary effect of undernutrition and weight loss on cardiac output and blood pressure. There is no evidence that rice contains a blood pressure-lowering principle. Animal experimentation has confirmed only that the diet leads to inanition and moderate reduction of the blood pressure in dogs.[59]

56 Himwich H E, Goldfarb and Nahum, L H. Changes of the Carbohydrate Metabolism of the Heart Following Coronary Occlusion, Am J Physiol 109: 403 1934. Caller R M. Effect of Nicotinic Acid on Myocardial Systole Coronary Flow and Arrythmias of Isolated Heart, Proc Soc Exper Biol. & Med. 65: 76 1947

57 Kempner W. Some Effects of the Rice Diet Treatment of Kidney Disease and Hypertension Bull. New York Acad Med. 22: 358 1946

58 Master A M, Strickler J, Grishman A and Dack S. Effect of Undernutrition on Cardiac Output and Cardiac Work in Overweight Subjects Arch. Int. Med. 69: 1010 (June) 1942

59 Dick, G F and Schwartz, W B. Response of Experimental Hypertension to a Rice and Fruit Juice Diet, Proc. Soc. Exper Biol. & Med. 65: 22 1947

A recent report[60] of the results obtained in a group of hypertensive patients using a low sodium (0.2 Gm per day) diet otherwise nutritionally sound confirms the value of sodium restriction in the treatment of hyper tension which may prove to be of greater value than sympathectomy

NUTRITIONAL NEEDS IN INFECTIOUS DISEASES

It is a common belief that malnourished" persons fall easy prey to infectious disease yet there is little strictly objective evidence to support this belief At present our knowledge is limited to the generality that host resistance' is reduced by malnutrition

Cannon[61] commented that, since the immune bodies of the serum are identified as globulins, a deficiency of *diet protein may lead to impairment of antibody produc* tion The experimental evidence to support this con tention is based on the response of rats in a state of extreme protein deficiency It remains to be shown whether the more chronic protein deficiency state seen *in man leads to similar changes Other workers have* been unable to demonstrate an alteration of resistance to natural infections by dietary protein deficiency of less extreme degrees in the rat[62] Recently Schneider[63] summarized experience with diet and resistance to *infection in mice It is concluded that there* is a demonstrable influence of diet on host resistance under certain conditions The nature of this relationship is yet little understood so that it is not possible to make clinical applications The effect of diet on resistance *would seem to be more subtle than manifest by* altera tion of circulating antibodies

Perhaps the most striking clinical evidence of the effect of nutrition on the course of an infectious disease is reflected in the remarkable fall of morbidity and mor tality rates of typhoid fever after the starvation regimen of therapy was replaced by nutritionally adequate diets A recent report[64] emphasized the importance of encour

60. *Bryant, J M and Blecha E. Low Sodium Forced Fluid Management of Hypertensive Vascular Disease and Hypertensive Heart Disease.* Proc. Soc. Exper Biol & Med. 65 ..7 1947
61 Cannon, P R. *Protein Metabolism and Acquired Immunity J Am.* Diet. A. 20 77 1944
62. Metcoff J Darling D B Scanlon, M H. and Stare, F J Nutritional Status and Infection Response, J Lab. Clin. Med. 33:47 1948
63 Schneider H. A. The "Yes" and "No" of Nutrition and Natural Resistance to Infectious Disease. Am. J Pub. Health 39 57 1949
64 Goodman, J I and Garvin, R. O Results of High Caloric Feeding. Gastroenterology 6:537 1946.

aging high caloric high protein diets during convalescence from infectious disease The problems of anorexia nausea and vomiting can often be surmounted by education and explanation to the patient that the diet is medical treatment for the disease The low caloric concentration of conventional liquid diets often defeats the purpose of a liquid diet regimen

Despite the clinical observations that convalescence in several infectious diseases is hastened by adequate diet the classic study of Grossman and his co workers[65] using the nitrogen balance technic indicates that a large negative nitrogen balance occurs with acute infectious diseases and that this wastage persists despite high protein and caloric intake The nature of this phenomenon is not understood The anemia of infection described by Cartwright and his co workers[66] in which anemia develops despite iron supplementation seems to be a related phenomenon The report of Croft and Peters[67] that the nitrogen wastage after thermal burns in rats could be significantly reduced by increases of dietary protein or by inclusion of 1 per cent of methionine suggests again that the limiting factor in convalescence may be one or a few essential substances

There is little quantitative evidence concerning the effect of fever on vitamin requirements Experimental evidence in rats[68] which seems to indicate that thiamine pyridoxine and choline requirements are increased by an increase of environmental temperature has not been completely elucidated Perhaps the best support for the inclusion of supplementary vitamins in the therapy of patients with infectious disease is the frequent observation that the florid deficiency states are often precipitated by an infectious disease Classic beriberi or pellagra are frequently seen as a complication of an infectious disease occurring in a previously malnourished person

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65 Grossman C M Sappington T S Burrows B A Lavietes P H and Peters J P Nitrogen Metabolism in Acute Infections, J Clin. Investigation 24:523 1945

66 Cartwright, G E Lauritsen M A Jones P J, Merrill, I M and Wintrobe, M M The Anemia of Infection J Clin Investigation (I) 25:65 1946 Cartwright, G E. Lauritsen, M A Humphreys, S, Jones P J Merrill I M and Wintrobe, M M The Anemia of Infection (II) J Clin Investigation 25:81 1946

67 Croft I B and Peters, R. A Nitrogen Loss After Thermal Burns Effects of Adding Protein and Methionine to Diet of Rats Lancet 1: 66 1945

68 Mill C A Metabolic Acclimatization to Tropical Heat, Nutrition Rev 3:317 1945

Of interest in a discussion of the relationship of diet to 'resistance" are the observations that manition or *thiamine deficiency* appear to improve the resistance of experimental animals to virus infections or virus incited tumors[69] There is no evidence to support the contention that administration of any or all of the vita mins to previously well nourished persons will increase "resistance' to infection

NUTRITIONAL NEEDS IN ENDOCRINE DISEASES

The treatment of diabetes mellitus is based on diet regulation The immediate objectives of diet therapy in diabetes are (1) to insure adequate nutrition, (2) to conserve the *limited insulin-producing mechanism* which remains and (3) to complement the regulation achieved with insulin

Although there has been considerable clinical and experimental study of this subject, there is no con clusive evidence to support the contention that dia betics have increased requirements for B complex vitamins and this despite the frequence of peripheral neuritis in diabetics which simulates a thiamine defi ciency neuritis but which is more likely related to the inevitable progression of peripheral vascular disease

The insurance of a nutritionally sound diet for dia betic persons almost certainly follows when diet therapy directed toward management of the endocrine disorder is commenced The avoidance of concentrated carbo hydrate foods the use of leafy vegetables fruits and whole grain cereals with daily servings of meat and eggs *furnish a sound diet Probably the most vulnerable* aspect of the diet is its calcium content A pint of milk daily should be a minimum allowance As in patients with ulcer diabetics should be taught the principles of diet selection and self management When this task is well done the diabetic person as Joslin has pointed out *is better off for his diabetes*

The protein requirements of persons with diabetes are not known to be abnormal so long as glycosuria is con trolled The National Research Council allowances for protein are adequate for the diabetic person

The most satisfactory level of fat in the diet is probably between *75* and *125* Gm per day although

69 Sprunt, D H The Effect of Undernour shm nt on the Suscepti b l ty of the Rabbit to Infect on with Vaccin a, J Exper Med. 75: 297 1942.

some workers, notably Rabinowitch,[70] believe that a low fat diet will delay and minimize the vascular sclerosis so characteristic of diabetes An average diet used by the Joslin group would contain 165 Gm carbohydrate, 83 Gm of protein and 97 Gm of fat This diet represents a conservative and probably the most widely used type of diet therapy in diabetes

A relatively recent innovation and one which remains unevaluated is the free diet regimen introduced in 1932[71] and in the past decade adopted by several clinics in this country This procedure attempts to prevent acidosis by using insulin without dietary restriction It has been particularly recommended for children when diet regulation may lead to psychiatric problems The narrow margin of safety from coma the persistent diuresis with consequent loss of electrolytes and calories and the potentially harmful effects of persistent hyperglycemia are all criticisms which may apply to this procedure Clinical evaluation will require many years of careful study

HYPERTHYROIDISM

The treatment of hyperthyroidism is directed toward correction of the metabolic defect Until the excessive rate of metabolism can be controlled either by chemotherapy or surgery or a combination of these procedures the principal dietary problem is one of supplying sufficient calories so that the body stores will not be drawn on. High calorie diets are indicated Carbohydrate and fat supplements to a normal protein allowance must be assured Often 5 000 to 6 000 calories may be necessary In so far as the caloric requirement is not met, the dietary protein and body protein will be diverted to energy channels and a protein deficiency state with loss of weight will ensue. The evidence for increased vitamin requirement in hyperthyroidism is based on animal experimentation principally with thiamine which indicates that thiamine requirements are related to total caloric exchange.

It has been reported that liver feeding alleviates experimental thyrotoxicosis in rats[72] The discovery of

70. Rabinowitch I M Prevention of Premature Arteriosclerosis in Diabetes Mellitus, Canad. M A. J 51:300 1944

71 Lichtenstein A. Treatment of Children's Diabetes Ten Years Experience Without Dietetic Restrictions Acta. med. Scandinav 32: (supp 1) 556 1944 1945

72 Ershoff B H Effects of Liver Feeding on Growth and Ovarian Development in the Hyperthyroid Rat, Proc. Soc. Exper Biol. & Med. 64:500, 1947

vitamin B_{12} led Nichol and his associates [73] to use vitamin B_{12} in place of liver It was found that this new vitamin protected thyrotoxic animals as well as did liver and other crude materials, thus suggesting another possible clinical application of this new vitamin Supplementary levels of B complex vitamins are indicated in thyrotoxicosis There is no evidence pertinent to fat-soluble vitamin requirements

CONCLUSION

A consideration of nutrition in illness and disease is important from the viewpoints of etiology, diagnosis therapy and prevention In our opinion nutrition is the most important single environmental factor affecting health

73 Nichol C A Dietrich, L S Cravens W W, and Elvehjem C A Activity of Vitamin B_{12} in the Growth of Chicks Proc. Soc. Exper Biol & Med 70 40 1949

Part III

NUTRITIONAL DEFICIENCIES

CHAPTER XVIII

IMBALANCE AND DIETARY INTER-RELATIONSHIPS IN NUTRITION

C. A. ELVEHJEM
and
WILLARD H. KREHL

One might define as the optimum goal of the nutritional biochemist the development of a diet which supplies all nutrients in respect to kind and amount and in proper state of combination for all physiologic processes from conception to the death of the organism. In addition the adequate diet must contain a minimum of injurious (toxic) factors Such a diet would indeed be balanced and any important deviation downward from the proper amount of a nutrient would lead to one well known kind of imbalance, reflected as deficiency disease. Since much has been written concerning this kind of imbalance, it will be considered here only incidentally

It is primarily when and where a variety and abundance of foodstuffs are available that one can apply the criteria of a balanced diet as far as knowledge permits Any situation whether due to economic political geographic or climatic reasons, which limits the food supply both as to choice and as to amount obviously allows a restricted application of the concept of a balanced diet Under such conditions the most compelling desire of the organism is for calories Whether the source of calories supplies the 'essential factors is largely a matter of happenstance It is perhaps a fortuitous physiologic fact that the requirement for some factors such as vitamin B_1 is somewhat reduced under conditions of caloric restriction When, however the sources of calories are limited primarily to a single food material such as polished rice or corn, we see nutritional imbalance" at its worst, with large numbers of people afflicted with beriberi and pellagra respectively

It is pertinent to consider for a moment the basis on which our present criteria for a balanced diet were arrived at Most of the fundamental knowledge concerning the requirements for the various known (and as yet some unknown factors) has been obtained through numerous and laborious studies with experimental animals In addition the clinician has made invaluable contributions by translating these experimental observations into practical studies with human patients As data accumulated from animal feeding experiments it became obvious that the quality of a ration could not be accurately ascertained on the basis of its chemical composition alone It became further evident that requirements for specific factors changed with alterations in diet composition and that many needed factors existed which were beyond the scope of available analytical chemical methods The employment of highly purified rations gave perhaps the greatest impetus to the search for an elucidation of unknown vitamins, until now it is proudly stated (although always with some reservation) that at least the qualitative nutritional requirements of certain species are known Several important lessons can be gleaned from the accumulated experimental data and are worth enumerating (*a*) the effectiveness of nutrition in maintaining optimum health depends on the inclusion in the diet of the least known as well as the best known nutrient (*b*) it is desirable to employ numerous species of animals in nutritional research, since nutritional requirements vary both in kind and in amount from species to species and (*c*) the application of accumulated experience to problems of human nutrition will certainly be on a firmer basis when the nutritional requirements of experimental animals are known

One of the important and practical achievements in nutrition is the development of the tables of recommended dietary allowances [1] prepared by the Food and Nutrition Board of the National Research Council These tables were developed largely by the application of ' cooperant reason to the numerous published nutritional observations on animals and human beings It will be noted that the board uses the term recommended allowances rather than standards to avoid any implication of finality ' It is difficult to make an adequate evaluation of the service that this board has rendered

1 Recommended Dietary Allowances (Revised 1948) National Research Council Reprint and Circular Series number 129 October 1948

since in addition to establishing certain 'yardsticks' of good nutrition it has intelligently focused attention on the ever important problem of adequate nutrition for all. That such attention is important is sadly apparent in the continued evidence for inadequate diets and nutritional deficiencies in the United States.[2]

Although "synthetic diets" have proved invaluable in determining what and about how much vitamin, amino acid or fatty acid is required by various animals, it is becoming increasingly apparent that the requirements for these specific materials both qualitatively and quantitatively can be definitely altered when fed as components of a foodstuff. That man can derive his nutrition, at least for a short time, on a synthetic diet is known.[3] However, for the most part man's diet is composed of natural materials and for this reason a new approach to nutritional research awaits further investigation, namely the study of the effect of these various materials and the kind and percentage of dietary components on the requirement of those factors which are required for the most part in relatively small amounts.

One potentially important aspect of the matter of altered vitamin requirement induced by natural materials is indicated by Woolley's[4] studies on certain relationships of chemical structure to biologic activity. It has been shown that certain chemical substances which have a structural relationship to various required biologic compounds may cause when administered, specific signs of deficiency diseases which can be reversed by the metabolites in question when given in adequate amounts.' Extensive evidence for the natural existence for such inhibitors is not available but this may be due primarily to lack of knowledge and experimental technics for demonstrating their existence. That such materials can exist under certain specified conditions is demonstrated by the vitamin K deficiency caused by dicumarin when spoiled sweet clover hay is eaten by cattle. It must be emphasized that the activity of these anti compounds is presumably due to the fact that they closely resemble the required biologic compound

2 Inadequate Diets and Nutritional Deficiencies in the United States, Bull National Research Council 100, November 1943

3 Olmstead, W. H., Hartford, C. G., and Hampton, S. F.: Use of a Synthetic Diet for Food Allergy and Typhoid, Arch. Int. Med. 73: 341 (April) 1944

4 Woolley, D. W.: Some New Aspects of the Relationship of Chemical Structures to Biological Activity, Science 100: 579, 1944

in chemical structure Whether all "inhibitor" materials operate via the mechanism postulated by Woolley remains to be proved.

Another general factor which may result in imbalance in nutrition is the presence of natural toxicants in food Materials in food whether naturally present or as the result of processing, such as fluorine selenium lead, arsenic and copper, appear high on the list of intoxicants which may seriously impair the physiology of the organism when they are ingested at too high a level The presence of the toxic agent gossypol in certain cottonseed meals must be considered when this feed is employed in animal rations Under the same category must be placed certain wheat glutens and wheat products which are known to produce the disease known as canine hysteria [5] It has been shown recently, however, that wheat flour is effective in producing this disease as a result of its treatment with agene (NCl_3), a common agent for bleaching and improving flour [6] Whether agene induces canine hysteria directly or because of changes it produces in the wheat gluten is not certain nor is it certain that additional factors are not involved

The fact that the consumption of certain legumes such as fava beans djenkol beans and lathyrus peas produce untoward results is well known and need not be discussed further

While the nutritional imbalance and biochemical defects due to such intoxicants can be readily produced, explanations of their mechanisms are not well known Even less understood are the changes in requirement and production of deficiencies and altered physiology which may result from seemingly innocuous modifications of such factors as the type of carbohydrate in the ration balance of inorganic elements amount and kind of protein or amino acid(s) qualitative and quantitative changes of fat and fatty acids in the diets and general vitamin level In addition one must consider the interrelationships known to exist between nutrients

The foregoing factors are known to induce 'imbalances' in nutrition which are considerably more difficult

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5 Wagner J R and Elvehjem C. A A Study of Canine Hysteria Produced by Feeding Certain Baked Dog Foods and Wheat Gluten Flour J Nutrition 28 431 1944 Melnick D and Cowgill G R. The Toxicity of High Gliadin Diets Studies on the Dog and on the Rat, ibid 14: 401 1937

6 Mellanby Edward Diet and Canine Hysteria Experimental Production Brit M J 2: 885 (Dec. 14) 1946

to explain than the mere omission of a specific required substance and these somewhat subtle changes will be considered at some length

MINERAL IMBALANCE

Because of the importance of calcium and phosphorus in nutrition some of the significant factors concerning their availability as affected by diet are worthy of consideration Of the important factors which favorably influence the absorption and utilization of calcium magnesium and phosphorus an acid reaction in the intestine ranks high in importance

That vitamin D is important in calcium utilization may be explained at least in part by the little understood fact that it tends to favor the production of an acid *pH* in the intestine. In this connection another recently elaborated role of vitamin D is the observation[7] that it has a favorable influence on the utilization of the phosphorus of phytin the availability of which has been the subject of considerable controversy

Moderate quantities of dietary fat may also play a favorable role in promoting an acid intestinal reaction Another dietary component which promotes such a reaction is lactose which probably mediates its influence through the establishment of an aciduric bacterial flora Is it not interesting that when the need for calcium and phosphorus assimilation is greatest (i e the growing child) the major normal dietary component is milk which is not only a good source of these minerals but contains lactose and is high in fat? Dextrin and corn starch also have an effect similar to but less than lactose.

Another important consideration concerning the possible imbalance of diets due to minerals is the significance of the calcium phosphorus ratio From the considerable work that has been done on this subject it may be concluded that both calcium and phosphorus may be lost from the body and excreted in the event of any decided abnormality of the calcium phosphorus ratio There is considerable variation in opinion as

7 Boutwell R. K Geyer R. P Halverson A W and Hart E. B The Availability of Wheat Bran Phosphorus for the Rat, J Biol. Chem. 162: 151 1946

to just what the optimum ratio should be, and it certainly varies with the nutritive requirement at different ages (i e from 1 5 1 to 2 1 for infants, to about 1 1 for older children)[8] Milk which may be considered a sound basis for good nutrition has a Ca P ratio of about 1 2 1

Other factors which may adversely affect calcium utilization are excessive amounts of magnesium in the diet and the well known calcium combining action of the oxalate in certain foods

In considering the other minerals which may interfere with phosphorus utilization one could conclude that certain cations such as iron and manganese for practical examples, which form insoluble phosphate compounds in the intestinal tract may if fed in sufficient concentration, lead to impaired phosphorus utilization Likewise excesses of phosphorus in the diet can interfere with the utilization of these cations McCance[9] for instance found that both phosphate and phytin interfered perceptibly with iron absorption although the effect of phosphate was not as great as that of phytate

In relation to calcium utilization, it was shown[10] that diets high in protein notably favored the absorption of calcium and also resulted in increased magnesium absorption This observation might have significance in locations where protein comprises a major portion of the diet and calcium intake is limited

The effect of a general mineral imbalance is well illustrated in the recent observation[11] that a partial substitution of casein with whey protein in a formula simulating human milk resulted in a retardation of rat growth This result was not in accord with the well known superior biologic value of lactalbumin (in whey) over casein This discrepancy was made clear however when by dialysis of the whey, its minerals were removed and more favorable growth ensued When the min

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8 Stearns Genevieve The Significance of the Retention Ratio of Calcium Phosphorus in Infants and in Children Am J Dis Child. **42** 749 (Oct) 1931

9 McCance R A Edgecombe C N and Widdowson E M Phytic Acid and Iron Absorption Lancet **2**: 126 (July 31) 1943

10 McCance R W Widdowson E M and Lehmann H The Effect of Protein Intake on the Absorption of Calcium and Magnesium, Biochem J **36** 686 1942

11 Daniel F K and Harvey E H Some Observations on the Nutritional Value of Dialyzed Whey Solids J Nutrition **33** 429 1947

erals which had been dialyzed from the whey were ashed and reintroduced in the ration, poor growth again resulted

INFLUENCE OF FATS

It has been indicated that dietary fat may assist in calcium and phosphorus utilization by favoring a more acid reaction in the intestinal tract In addition it is increasingly apparent that fats may have other important roles in nutrition beyond the fact that they assist in the absorption of and act as carriers for the fat soluble vitamins The human body can utilize 93 to 98 per cent of most common fats and it can tolerate quantities of fat equivalent to at least a third of the average daily energy consumption[12] No definite opinion has been crystallized as to the optimum level of dietary fat suggestions have been made favoring levels just sufficient to supply the essential fatty acids up to an amount equivalent to 25 or 30 per cent of the daily intake Even greater divergence of opinion is evident concerning the type of fat which should be employed in the diet The numerous controversial observations[13] regarding the nutritional superiority of butter fat over certain vegetable fats are sufficient to illustrate this point The recent report[14] that vaccenic acid (C18 Δ 11 12 elaidinic acid) present in summer butter has growth promoting properties offers the most concrete evidence to date in support of butterfat superiority for rat growth It remains to be seen whether this observation will be confirmed or lead to further controversy

Boutwell and his associates[15] in extensive experiments have consistently observed that when lactose is used as the sole carbohydrate or when the general level of B complex vitamins is employed at a comparatively low level butterfat is superior to corn oil in effecting rat growth Even greater growth differences were evident when younger rats (less than 21 days old)

12 Longworthy C A. The Digestibility of Fats J Indust. & Engin Chem. 15:276 1923

13 Deuel H J Jr Movitt E. Hallman L. F and Mattson, F Growth Rate and Efficiency of Conversion of Various Diets to Tissue J Nutrition 27:107 1944 Boutwell Geyer Elvehjem and Hart.[15]

14 Boer J Jansen, B C. P and Kentie A. On the Growth Promoting Factor for Rats Present in Summer Butter J Nutrition 33:339 1947

15 Boutwell R. K Geyer R P Elvehjem C A and Hart, E. B Further Studies on the Comparative Value of Butter Fat, Vegetable Oils and Oleomargarines J Nutrition 26:601 1943

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8 Stearns Genevieve The Significance of the Retention Ratio of Calcium Phosphorus in Infants and in Children Am J Dis Child. **42** *749* (Oct.) 1931

9 McCance R A Edgecombe C N and Widdowson E M Phytic Acid and *Iron Absorption Lancet 2 126 (July 31) 1943*

10 McCance R W Widdowson E M and Lehmann H The Effect of Protein Intake on the Absorption of Calcium and Magnesium Biochem J **36** 686 1942

11 Daniel F K and Harvey E H Some Observations on the Nutritional Value of Dialyzed Whey Solids J Nutrition **33** 429 1947

in this connection that milk, a high fat food, is one of the richest natural sources of riboflavin

The thiamine sparing action of fat has been adequately reviewed,[21] but in view of recent experiments[22] this sparing action must be considered with somewhat greater reservation since it can be shown that the young growing rat develops the typical symptoms of polyneuritis actually more clearly on B_1 deficient high fat diets than on isocaloric carbohydrate diets. This observation is certainly more consistent with the increasing evidence in support of the tricarboxylic acid cycle as a pathway for the oxidation of fatty acids as well as carbohydrate. This being the case thiamine should be as important in fat metabolism as in carbohydrate metabolism.

Evidence is also available[22] which indicates that the growth of rats on pantothenic acid deficient diets can be greatly improved by the isocaloric replacement of the carbohydrate of the diet with fat In addition the difference obtained is greater when the protein level of the diet is high than when it is low

On the other hand the severe skin symptoms of egg white induced biotin deficiency can be produced much more rapidly when fat replaces the carbohydrate[22] This cannot be considered as a direct adverse effect of fat because in this case the skin symptom evidences of the biotin deficiency appear more quickly probably because the rat s growth rate is better on the high fat diet and hence the stores of the vitamin are exhausted sooner

The recent demonstration[23] that a niacin deficiency in the rat is more readily produced on a low fat diet and that 30 per cent of fat in the diet tends to counteract this deficiency is another example of the vitamin sparing action of fat

It was observed early in the work on vitamin B_6 that the acrodynia symptoms associated with this deficiency were more apparent when fat was omitted from the diet This observation was more particularly related to the

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21 Cowgill G R. The Vitamins, Chicago, American Medical Association, 1939 pp. 159-1 8.
22. Krehl, W A. and Carvalho, A. Unpublished data.
23 Salmon W D Some Physiological Relationships of Protein, Fat, Cholin Methionine, Cystine Nicotinic Acid and Tryptophan, J Nutrition 33:155 1947

were used at the start of the experiment[16] Certainly, some of the observed differences between butterfat and corn oil may be explained on the different effects of these respective fats on the intestinal flora

To present the other side of this controversy, Deuel and his associates[17] observed that "if fat per se is required for fertility and pregnancy, its requirement may be equally satisfied by the various vegetable fats as by butter From the standpoint of lactation, as judged by the survival of the litter and the weight of the young at weaning time, the different fats were also equally effective Interesting as this problem is, its final solution can be reached only through further research

Perhaps more pertinent to the topic under consideration is the relationship between dietary fats and other nutrients For example, the presence of rancid fat in the diet produces some interesting effects which deserve mention From the accumulated literature on this subject it appears that there is significant destruction of vitamin A as a result of rancid dietary fat This destruction seems to be associated with intense peroxide formation although it has been concluded[18] that intermediates of fatty acid peroxidation are the active agents involved and not the peroxides themselves It has been shown too[19] that oxidative changes which accompany the development of rancidity in unsaturated fats destroy vitamin E

That high fat diets exhibit a striking effect on the requirement of certain members of the B complex is well known Mannering[20] has shown for example that fat at a level of 25 and 40 per cent of the diet materially increased the riboflavin requirement of the rat This effect may be mediated through the impairment of riboflavin synthesis by intestinal bacteria as an unfavorable result of the high fat level It is interesting to note

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16 Boutwell R K Geyer R P Elvehjem C A and Hart E B Further Studies on the Growth Promoting Value of Butt r Fat, J Dairy Sc **26** 429 1943

17 Deuel H J Jr Movitt E and Hallman L F The Negative Effect of Different Fats on Fertility and Lactation in the Rat J Nutrition **47** 509 1944

18 Sumne R J The Relation Between Carotene Oxidation and the Enzym c Peroxidat on of Unsatu ated Fats J B ol Ch m. **146** 215 1942

19 Matt ll H A The Oxidative Destruction of Vitamins A and E J A M A **89** 1505 (Oct 29) 19 7

20 Mannering G J Or ni D and Elvehjem C A Effect of the Composition of Diet on the Riboflavin Requirement of the Rat J Nutrition **28**: 141 1944

or, more specifically, of galactose Geyer and his associates[27] in more recent experiments on this subject, conclude that (*a*) fat in some way influences galactose utilization (*b*) galactose utilization is appreciably decreased as the percentage in the diet is increased and (*c*) added glucose does not lower galactose excretion as does fat

Since approximately 50 per cent of the calories of whole milk are derived from fat it is obvious that the use of milk as the sole source of calories will not result in physiologic embarrassment due to the failure of galactose utilization (except in certain rare cases) Nature would indeed be cruel to permit anything but this condition to exist since infants in particular obtain nearly all their calories from milk

Handler[28] writing on this subject considers that there is a biochemical defect which underlies the failure of lactose (galactose) utilization and indicates that this is due to an impairment of normal glucose metabolism, although no definite statement is given as to the nature of this disturbance

One must consider that at high levels of galactose ingestion the ability of the organism to convert galactose to glucose is rapidly exceeded in which event the excess is excreted The only biochemical defect" then according to this interpretation would be one of over dosage

Whether or not fat or any of the intermediates of fat metabolism exert a biochemical note in the reactions involved in the conversion of galactose to glucose to glycogen can be ascertained only after additional research

CARBOHYDRATE RELATIONSHIPS TO VITAMIN REQUIREMENTS

As a readily available and most economical source of energy carbohydrate is of primary importance in nutrition About 50 or 60 per cent of the calories of the average diet[1] are derived from carbohydrate although wide deviations from this amount are possible witness the low carbohydrate intake of the Eskimo

27 Geyer R. P Boutwell R. K Elvehjem, C A and Hart, E. B The Effect of Fat on the *Utilization of Galactose by the Albino Rat*, J Biol Chem. 162:251 1946

8. Handler P The Biochemical Defect Underlying the Nutritional Failure of Young Rats on Diets *Containing Excessive Quantities of Lactose or Galactose* J Nutrition 33:221 1947

presence of certain fatty acids in the diet, especially linoleic acid

The relationship between high fat diets and the requirement of choline and labile methyl groups is indicated by the fact that a simultaneous deficiency of these two factors in high fat diets results in more rapid fatty infiltration and necrosis of the liver with frequent findings of hemorrhagic degeneration of the kidney

It is understandable that the numerous favorable effects of high fat diets should be interpreted from the point of view of the known role of certain of the B complex vitamins involved in carbohydrate metabolism but to assume that these vitamins are not as important in the metabolism of fat may be merely a reflection of our ignorance of the biochemical transformations involved in the ultimate break down of fat

A fresh point of view concerning the value of fat in the diet is based on the finding of Forbes and his associates [24] that on a mixed diet containing fat, animals have extra calories for work growth or storage These extra calories are not available when fat is omitted from the diet even though an isocaloric mixture of carbohydrate and protein is supplied Fat apparently confers efficiency of utilization of food energy on both growing and mature rats The observed retention of nitrogen as tissue protein was over 10 per cent greater on a 30 per cent than on a 2 per cent fat diet In other words the energy cost of metabolizing diets providing constant protein intake decreased with increasing ratio of fat to carbohydrate Deuel [25] has recently concluded that the favorable effect of diets containing fat is due to several factors (*a*) the greater intake in terms of energy values of diets containing fat and (*b*) greater efficiency of utilization

The value of dietary fat in the utilization of certain carbohydrates is indicated from the work of Schantz and his associates [6] who showed that the 3 or 4 per cent of fat naturally present in milk is necessary if the animal is to make complete utilization of the lactose

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24 Forbes E B Swift R W Elliott R F and James W H Relation of Fat to Economy of Food Utilization I By the Growing Albino Rat J Nutrition **31** 203 1946

25 Deuel H J Jr Meserve E R Straub E Hendrick C and Scheer B T The Effect of Fat Level of the Diet on General Nutrition J Nutrition **33** 569 1947

26 Schantz E J Elvehjem C A and Hart E B The Relation of Fat to the Utilization of Lactose in Milk J Biol Chem. **122** 381 1942

or, more specifically, of galactose Geyer and his associates[47] in more recent experiments on this subject, conclude that (a) fat in some way influences galactose utilization (b) galactose utilization is appreciably decreased as the percentage in the diet is increased and (c) added glucose does not lower galactose excretion as does fat

Since approximately 50 per cent of the calories of whole milk are derived from fat it is obvious that the use of milk as the sole source of calories will not result in physiologic embarrassment due to the failure of galactose utilization (except in certain rare cases) Nature would indeed be cruel to permit anything but this condition to exist since infants in particular obtain nearly all their calories from milk

Handler[48] writing on this subject considers that there is a biochemical defect which underlies the failure of lactose (galactose) utilization and indicates that this is due to an impairment of normal glucose metabolism although no definite statement is given as to the nature of this disturbance.

One must consider that at high levels of galactose ingestion the ability of the organism to convert galactose to glucose is rapidly exceeded in which event the excess is excreted The only biochemical defect then according to this interpretation would be one of over dosage.

Whether or not fat or any of the intermediates of fat metabolism exert a biochemical note in the reactions involved in the conversion of galactose to glucose to glycogen can be ascertained only after additional research.

CARBOHYDRATE RELATIONSHIPS TO VITAMIN REQUIREMENTS

As a readily available and most economical source of energy, carbohydrate is of primary importance in nutrition About 50 or 60 per cent of the calories of the "average diet" are derived from carbohydrate although wide deviations from this amount are possible, witness the low carbohydrate intake of the Eskimo

[47] Geyer R. P., Boutwell R. K., Elvehjem, C. A., and Hart, E. B. The Effect of Fat on the Utilization of Galactose by the Albino Rat J Biol. Chem. 162:251 1946

[48] Handler P. The Biochemical Defect Underlying the Nutritional Failure of Young Rats on Diets Containing Excessive Quantities of Lactose or Galactose, J Nutrition 33:221 1947

and the reduced intake of the person with diabetes Using milk as a nutritional standard again it can be seen that in this food carbohydrate comprises only about 30 per cent of the total calories McCollum[29] states that "the minimum amount of carbohydrate necessary for maintenance of life and the prevention of ketosis is from 10 to 15 per cent of the total energy requirement" Species variation may modify these figures to some extent

Aside from observations, such as the different absorption rates of hexose sugars[30] the general unavailability of pentoses and cellulose for man, and the aforementioned findings concerning galactose and lactose, very little information is available concerning the comparative nutritional qualities of the several types of carbohydrate which man can utilize

It is indeed a fortuitous economic fact that ruminants such as the cow have a type of digestive system which permits utilization of a substantial portion of dietary cellulose This fact is a result of the favorable action of cellulose digesting organisms in the rumen which are capable of breaking down cellulose to available hexoses

This particular mechanism of bacterial action is not present in the human digestive tract but another type of bacterial synthesis can undoubtedly act in a beneficial manner for man The extent to which a favorable bacterial synthetic mechanism can assist man in supplying certain factors may depend very importantly on the type of carbohydrate employed in the diet if the experiments with animals can serve as a guide Fridericia[31] was the first to observe that animals can grow satisfactorily on certain diets deficient in the 'B vitamin This condition, known as refection can be readily produced by giving diets which contain raw potato starch as the carbohydrate Cooked potato starch on the other hand does not cause refection These observations have been confirmed by numerous workers and

29 McCollum E V Orent Keiles E and Day H G The Newer Knowledge of Nutrition Macmillan Company New York 1939

30 Cori C F and Cori G T The Influence of Insulin on the Utilization of Glucose Fructose and Dihydroxyacetone J Biol. Chem. 76 755 1928

31 Fridericia L S Refection a Transmissible Change in the Intestinal Content Enabling Rats to Grow and Thrive Without B Vitamin in Food Skand nav arch f physiol 49 129 1926

extended applications of the phenomenon have been made.

The fact that the growth and appearance of experimental animals on diets deficient in certain members of the B complex vitamins can vary considerably depending on the type of carbohydrate used indicates that there are decided differences in the nutritional value of carbohydrates not reflected by their similar energy values.

Results common to all the experiments that will be cited can be summarized by saying that regardless of which vitamin was investigated its requirement was reduced in all cases when relatively insoluble carbohydrates such as dextrin or starch were used in the diet Lactose has also given similar results in many cases although not so accentuated and surprisingly enough in some cases diets containing glucose have favorably influenced the vitamin requirement In all cases when sucrose was the dietary carbohydrate of choice the vitamin requirement was highest One might place the carbohydrates in the following decreasing order in their favorable effect on vitamin requirement dextrin starch lactose glucose sucrose although this varies with different vitamins

It seems reasonable to the proponents of the mechanism of intestinal synthesis that certain carbohydrates, owing to their slower breakdown and absorption from the intestinal tract provide a suitable substrate for the development of a type of bacterial flora which may contribute significant quantities of vitamins to the host. Mannering[24] states for example that "when the riboflavin intake is suboptimal rats receiving a diet rich in dextrin or corn starch show greater weight increases than do animals receiving diets characterized by their content of sucrose cellulose lactose or lard Lactose is not entirely without effect in this respect"

In a recent study Krehl and Carvalho[22] showed that the use of dextrin in pantothenic acid deficient diets greatly improved rat growth This favorable synthesis of pantothenic acid could be correlated with higher levels of this vitamin in cecal contents liver and muscle tissue and could be further related to much less hypertrophy and hemorrhage of the adrenal and better protection against involution of the thymus in comparison with deficient animals which received sucrose as the carbo-

hydrate. Likewise the onset of symptoms of egg white induced biotin deficiency were delayed when dextrin was used as the carbohydrate instead of sucrose, despite the fact that the dextrin fed rats grew better, which would tend to increase the demand for biotin

Good evidence is available [32] to support the idea that pyridoxine is synthesized by intestinal bacteria when the sucrose of the diet is replaced by dextrin That this mechanism may be available to man may in part explain the limited evidence for pyridoxine deficiency in this species

In a study on the effect of diet on the response of chicks to folic acid Luckey and his associates [33] report that the response to folic acid was least with high fat diets or with diets containing glucose sucrose or starch as the sole carbohydrate The best response to the vitamin was obtained with high protein, low fat diets or with diets containing corn meal or dextrin It is difficult to ascertain why in this case differences between corn starch and corn meal and dextrin were observed A possible explanation might be due to the rather undesirable physical aspects of diets high in corn starch It seems that several interrelating factors may be involved in influencing the effect of diet on the folic acid requirement of the chick.

Such a complexity between diet composition and vitamin requirement is well demonstrated in the interesting series of experiments [34] which have established certain conditions under which a niacin deficiency can be induced in the rat an animal which had normally been considered not to require a dietary source of this vitamin

It was first shown that if 40 parts of the sucrose of a synthetic ration are replaced with corn grits the niacin requirement of the growing dog is increased from about 0 3 mg per kilogram of body weight to about 1 mg despite the fact that corn grits contribute some niacin to the diet When this

32 Sarma, P S Snell, E. E., and Elvehjem, C. A The Vitamin B₆ Group VIII Biological Assay of Pyridoxal Pyridoxamine and Pyridoxine J Biol Chem. 165 55 1946

33 Luckey T D Moore P R. Elvehjem, C A. and Hart, E. B The Effect of Diet on the Response of Chicks to Folic Acid, Proc. Soc. Exper Biol. & Med. 62 307 1946

34 Krehl Sarma, Teply and Elvehjem.[illegible] Krehl Sarma and Elvehjem.[illegible] Krehl, de la Huerga and Elvehjem.[illegible] Krehl Henderson de la Huerga and Elvehjem.[illegible]

study was extended to the rat by replacing 40 per cent of a synthetic diet with corn or corn grits, which reduced the casein level of the corn supplemented diet to 9 per cent a retardation of growth was demonstrated This growth depression could be completely counteracted by the further addition of niacin to the diet, again despite the fact that in these experiments the corn and corn grits contributed 0 8 and 0 4 mg of niacin per hundred grams of diet respectively

It was recognized in this work that rat growth on a 9 per cent casein synthetic diet deficient in niacin is not optimum and generally is improved by the addition to the diet of amounts of niacin up to 1 mg per hundred grams If by this addition of niacin growth is improved why does not a similar amount of niacin as represented in corn grits, for example likewise improve growth particularly when one considers that the total protein and type of carbohydrate contributed by the corn should have some supplementary action to the diet? Actually a growth depression can be observed

Although the foregoing observations have been confirmed in other laboratories a criticism [35] has been made of these findings on the basis that the growth of rats is poor on a 9 per cent casein diet with or without the inclusion of corn and therefore corn has no "specific deleterious effect" In fact in this particular experiment the growth results obtained on the basal 9 per cent casein diet were so poor (less than 3 Gm per week for eight weeks) as to obviate a very fair comparison It is interesting to note though that in these experiments the addition of crystalline niacin also evoked a better growth response than did corn alone, which again is difficult to explain since in some of these cases at least nearly as much niacin must have been contained in the added corn as was added in crystalline form Whether or not corn has a specific deleterious action quite largely depends on extenuating circumstances If under defined conditions one compares corn with certain other cereal grains such as polished rice which closely resembles corn in its niacin and tryptophan content (to be discussed) one finds corn

35 Salmon W D Relation of Corn Products to the Requirement of the Rat for Nicotinic Acid, J Nutrition 33 169 1947

decidedly inferior, using the growth of young rats as a criterion Further evidence for the observed action of corn rations is indicated by the demonstration that corn contains a pellagragenic agent which can be extracted and prepared in fairly high concentration This "pellagragenic material" from corn when fed to mice produced a manifest growth depression Interestingly, corn alone does not have this effect in mice[36]

PROTEINS AND AMINO ACIDS IN NUTRITIONAL IMBALANCE

In studying the effect of corn on the growth of rats it was soon learned that when the casein level of the diet was increased good growth resulted whether or not corn was used in the diet This seemed to indicate that in conjunction with the niacin deficiency a concomitant amino acid deficiency might be involved Since corn is notably deficient in tryptophan, this amino acid was added to the corn supplemented ration and surprisingly enough proved to be as effective as niacin in promoting growth This fact indicated then an interrelationship between a vitamin niacin, and an amino acid tryptophan As already stated, rather specific conditions are needed for the production of this niacin deficiency in the rat When, for example dextrin corn starch itself or even glucose is used as the dietary carbohydrate in place of sucrose there is little growth inhibition from corn A low general level of vitamins accentuated the action of corn rations in retarding rat growth The favorable effect of a carbohydrate such as dextrin has been interpreted as being due to the establishment of an intestinal flora which augments niacin synthesis Since, as has been mentioned high levels of dietary fat tend to reduce the niacin requirement of the rat[25] the inclusion of 30 per cent of fat in the diet largely but not entirely eliminates the growth retardation induced by corn[35] Whether this effect can be likewise observed in man whose requirement for niacin is probably much higher than that of the rat must be questioned, particularly in view of the fact that pellagra producing diets in the South generally contain liberal amounts of fat from sowbelly'

36 Woolley D W The Occurrence of a Pellagragenic Agent in Corn J Biol Chem **163**:773 1946

A recent extension of the effect of corn rations on the niacin requirement has been made with the pig[37] in which it was observed that the use of corn as a major part of the ration resulted in a niacin deficiency even though the percentage of dietary protein was relatively high. "The supplementation of the low protein corn rations with tryptophan produced animals whose external appearance was normal in every respect." This supplementation also resulted in increased efficiency of food utilization.

Perhaps more interesting than the effect of corn supplemented rations on the dietary niacin-tryptophan requirement of the rat are the observations[38] that a completely analogous syndrome can be produced by adding tryptophan-free proteins or acid hydrolysates of protein (tryptophan free) to basal rations which contain 9 per cent casein and no niacin. For example, a protein such as zein, the chief protein from corn, when added to such a ration at a level of 3 per cent produces a niacin deficiency in the rat which can be completely counteracted by either tryptophan or niacin. The addition of gelatin at levels of 3 or 6 per cent produces a similar result.

What are the peculiarities of the amino acid mixture in acid hydrolysates of protein or the amino acid makeup of tryptophan-free proteins that induce such effect? No precise answer can be given on this point although it has been shown that the amino acid aminoacetic acid (glycine) is one (of perhaps many) which is capable of inducing an increased niacin requirement in the rat. Evidence is available[39] however to show that this growth inhibiting effect due to amino acids is not specific for any one particular amino acid but may in fact be produced by a mixture of synthetic amino acids equivalent to 2 per cent of an acid hydrolysate of casein. It is possible that the growth inhibition may be due

37 Luecke, R. W., McMillan, W. N., Thorp, F., Jr., and Tull, C. The Relationship of Nicotinic Acid, Tryptophan and Protein in the Nutrition of the Pig. J. Nutrition 33: 251, 1947.

38 Krehl, W. A., Sarma, P. S., Teply, L. J., and Elvehjem, C. A. Factors Affecting the Dietary Niacin and Tryptophan Requirement of the Growing Rat. J. Nutrition 31: 85, 1946. Krehl, W. A., Sarma, P. S., and Elvehjem, C. A. The Effect of Protein on the Nicotinic Acid and Tryptophan Requirement of the Growing Rat. J. Biol. Chem. 162: 403, 1946. Krehl, W. A., Henderson, L. M., de la Huerga, J., and Elvehjem, C. A. Relation of Amino Acid Imbalance to Niacin-Tryptophan Deficiency in Growing Rat. ibid. 166: 531, 1946.

39 Henderson, L. M., Deodhar, T., Krehl, W. A., and Elvehjem, C. A. J. Biol. Chem., to be published.

to alterations in the intestinal flora, since the effect of aminoacetic acid is eliminated when dextrin is used as the carbohydrate in place of sucrose Of course a mechanism involving tissue synthesis of niacin might very well be involved, or perhaps both of these mechanisms are concerned in this complex interrelation ship between niacin and tryptophan Only additional research can answer these questions

That other species are susceptible to the effects described can be seen from work with chicks[40] in which it was shown that the niacin requirement of the chick was influenced by the kind and amount of protein used in the ration Gelatin produced unfavorable growth results when niacin was omitted from the diet and this growth depression could be completely counter acted with either tryptophan or niacin When combinations of the amino acids arginine aminoacetic acid and alanine were used, niacin deficiency symptoms were also produced

No definite evidence is as yet available which com pletely elucidates the mechanism of the niacin tryptophan relationship As stated certain evidence strongly sup ports the idea that the intestinal flora may contribute importantly to niacin synthesis Another line of evidence has been advanced which supports the con tention that tryptophan may serve as a metabolic pre cursor of niacin This is based on the finding[41] that the excretion of N^1 methylnicotinamide the chief urinary excretory product of niacin metabolism is much increased following the administration of l(-) or dl tryptophan to the rat Such a hypothesis is certainly attractive, and the correlation between N^1-methylnicotinamide excretion and tryptophan inges tion has been extended to a number of species, including man Work with Neurospora mutants however has so far failed to establish any direct mechanism or metabolic pathway from tryptophan to niacin[42] although a relationship between this vitamin and tryptophan simi

40 Briggs G M Groschke A. C and Lillie R J Effect of Proteins Low in Tryptophan on Growth of Chickens and on Laying Hens Receiving Nicotinic Acid Low Rations J Nutrition **32** 659 1946

41 Rosen F Huff J W and Perlzweig W A The Effect of Tryptophan on the Synthesis of Nicotinic Acid in the Rat J Biol Chem **163** 343 1946

42 Bonner David and Tatum E. L. Personal communication to the authors

lar to the rat and other species is well established for certain of these mutants This of course does not prove that a direct synthesis of niacin from tryptophan does not exist

The recent observation[43] that pyridoxine deficient animals excrete less N[1] methylnicotinamide after the administration of tryptophan may help to throw some light on the indicated metabolic conversion of tryptophan to niacin and at least 'indicates that the normal formation of xanthurenic acid in B_6 deficiency is not responsible for the impaired tryptophan to nicotinic acid transformation This observation might in a sense be considered an extension of the earlier study by Singal and his associates who observed an increased excretion of N[1] methylnicotinamide as a result of administering pyridoxine to normal and niacin deficient dogs

It might be pointed out that since niacin may exert a tryptophan sparing action possibly because of its favorable influence on tryptophan utilization[44] the administration of tryptophan might correspondingly spare or reduce the metabolic need for the vitamin so that the excess not needed for other purposes is then methylated and excreted

Aside from the theoretical aspects of why both tryptophan and niacin have similar growth promoting effects, it is gratifying to note that recent experiments with human beings[45] indicate that tryptophan may be an important precursor of nicotinic acid in the human as well as the rat and may explain the antipellagragenic activity of certain foods such as milk which are low in nicotinic acid but rich in good protein' It might be noted that here no consideration is given to the known favorable effect of milk on the synthetic mechanism of the bacterial flora in experimental animals at least

The relationship between proteins or amino acids and vitamins is also indicated in the evident importance of pyridoxine in the metabolism of amino acids The vitamin B_6 group of vitamins has been shown to be

43 Rosen F Huff J W and Perlzweig W A The Role of B_6 Deficiency in the Tryptophan Niacin Relationship in Rats J Nutrition **33**: 561 1947

44 Krehl W A, de la Huerga J and Elvehjem C A Tryptophan Stud **4** The Effect of Niacin on the Utilization of Tryptophan J Biol. Chem **164** 551 1946

45 Sarett H I and Goldsmith G A The Effect of Tryptophan on the Excretion of Nicotinic Acid Derivatives in Humans J Biol Chem. **167**: 293 1947

important in two fundamental reactions involving amino acids (a) catalyzing transamination[46] and (b) catalyzing the decarboxylation of certain amino acids[47]

A specific role of pyridoxine seems to be involved in tryptophan metabolism,[48] in which case the administration of 1(-)tryptophan to pyridoxine deficient rats results in the excretion of xanthurenic acid rather than kynurenic acid the normal end product of tryptophan metabolism Kynurenic acid and more interestingly d(+) tryptophan do not lead to xanthurenic acid excretion in B_6 deficiency, xanthurenic acid passes through the pyridoxine deficient rat unchanged

That the level of dietary protein is important in determining the pyridoxine requirement is evident from the observation[49] that a diet containing a 60 per cent level of casein produced much earlier death in mice than one in which the protein level was 10 per cent "Although pyridoxine restored growth and minimized the excretion of chromogen on both diets about three times as much pyridoxine was required on 60 per cent of casein as when 20 per cent was fed"

Because of the ever increasing interest in the use of synthetic amino acids in nutritional studies, some mention must be made of certain recent experiments made with these materials The long chain of research on the qualitative and quantitative amino acid requirement stemming mostly from the laboratory of Rose has culminated in the successful use of diets which can be entirely characterized in regard to their amino acid makeup As might be expected with such relatively short time experience with amino acids there is no complete agreement as to the number or relative amounts of the so called 'essential amino acids required by the various species studied Clarification of these disagreements should come rapidly as a result of the intensive research in this field A generalization that might be made concerning amino acids and their application in

46 Schlenk F and Snell E F Vitamin B and Transamination J Biol Chem 157 425 1945

47 Gunsalus I C and Bellamy W D A Function of Pyridoxal J Biol Chem 155 357 1944

48 Reid D F Lepkovsky S Bonner E and Tatum E L The Intermediary Metabolism of Tryptophan in Pyridoxine Deficient Rats J Biol. Chem 155 299 1944

49 Miller E C and Baumann C A Relative Effects of Casein and Tryptophan on the Health and Xanthurenic Acid Excretion of Pyridoxine-Deficient Mice J Biol Chem. 157 551 1945

nutr[illegible] animals this can be gained from the observation[50] that rats fed a mixture of amino acids gained weight rapidly and usually exhibited weight gains in ten days as great as those given an equivalent nitrogenous quantity of casein. The omission of any of the essential amino acids from the diet resulted in a prompt loss in appetite followed by a weight loss. It must be noted however that these experiments were conducted with adult rats, and evidence is available[51] which shows that the young growing rat does not do as well on mixtures of amino acids as on casein in equivalent amounts. Further evidence of this nature is observed with mice and the factor which induces better growth under these conditions has been designated strepogenin,[52] which is apparently the material found in certain intact proteins or enzymatic protein hydrolysates. Whether this factor has practical significance in human nutrition is difficult to ascertain. It is known however, that properly prepared mixtures of the crystalline amino acids are adequate for the protein nitrogen needs and definite weight gain of patients over long periods of time. Given parenterally as the sole source of protein nitrogen intake, these amino acids are adequate for nitrogen balance in human patients[53] In these same experiments no toxicity to the unnatural forms of seven essential amino acids could be demonstrated. Although the amino acids were generally well tolerated when given parenterally, phenylalanine had a definitely limited effect on tolerance. It has been shown however[54] that mixtures of natural amino acids can be given to dogs at a much higher intravenous rate without inducing vomiting than can similar mixtures containing racemic amino acids. In these experiments aminoacetic acid increased the dog's tolerance to the infusion of certain of the mixtures containing racemic amino acids.

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50 Frazier, L. E., Wissler, R. W., Steffee, C. H., Woolridge, R. L., and Cannon, P. R.: Studies in Amino Acid Utilization. I. The Dietary Utilization of Mixtures of Purified Amino Acids in Protein Depleted Adult Albino Rats. J. Nutrition 33:65, 1947.

51 Henderson, L. M., Krehl, W. A., and Elvehjem, C. A.: Unpublished work.

52 Woolley, D. W.: Some Correlations of Growth Promoting Powers of Proteins with Their Strepogenin Content. J. Biol. Chem. 162:383, 1946.

53 Madden, S. C., Bassett, S. N., Remington, J. H., Martin, F. J. C., Woods, R. R., and Shull, F. W.: Amino Acids in Therapy of Disease. Surg. Gynec. & Obst. 82:131, 1946.

54 Howe, E. E., Unna, K., Richards, G., and Seeler, A. O.: Comparative Tolerance to Mixtures of Natural and Racemic Amino Acids on Intravenous Infusion in the Dog. J. Biol. Chem. 162:395, 1946.

important in two fundamental reactions involving amino acids (*a*) catalyzing transamination [46] and (*b*) catalyzing the decarboxylation of certain amino acids [47]

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46 Schlenk F and Snell E E Vitamin B₆ and Transamination J Biol Chem **157** 4 5 1945

47 Gunsalus I C and Bellamy W D A Funct on of Pyridoxal J Biol Chem **155** 357 1944

48 Reid D F Lepkovsky S Bonner E and Tatum E L The Intermed ary Metab lism of Tryptophan in Pyridoxine Deficient Rats J Biol. Chem **155** 299 1944

49 Miller E C and Baumann C A. Relative Eff cts of Casein and Tryptophan on the Health and Xanthurenic Acid Excretion of Pyridoxine Deficient Mice J B ol Chem. **157** 551 1945

Lack of agreement is evident concerning the unde sirable effects of the unnatural forms of certain amino acids for rat growth Factors such as the relative amount of the respective amino acid used and the type of carbohydrate employed in the diet may explain a large part of the differences observed Most of the evidence supports the contention that the unnatural forms of the essential amino acids at least do not sig nificantly impair the animal's performance It has been shown that dl serine, unlike the natural isomer produces proteinuria kidney and liver damage and high mor tality in rats [55] Interestingly enough, the administration of ample amounts of B vitamins substantially reduced these effects Of the vitamins tested pyridoxine proved most effective in its protective action against dl serine

Another point of disagreement has arisen as a result of the several studies on the relative lipotropic efficacy of methionine when fed as the free amino acid and as a constituent of an intact dietary protein A reason able explanation for the conflicting conclusions and well illustrative of the present theme that many inter related factors may alter the dietary requirement is offered in the finding that essential amino acids have a definite effect on the lipotropic efficacy of methionine [56] 'No significant difference was noted in the lipotropic effect exerted by methionine when fed as the free amino acid or in casein provided the essential amino acids were approximately equalized in the two diets "

The great interest in amino acids has revived in large measure the older problem concerning the biologic value of proteins The studies on this problem may in general be summarized by the observation [57] that 'the compari son of the chemical and biologic methods supports the hypothesis that the biologic value of a protein is due to its content of essential amino acid and is limited by the one essential amino acid which is present in the least amount relative to body requirements ' One of course should add that as indicated earlier other components of the diet may play an important role in

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55 Fishman W N and Artom C. Some D etary Factors Wh ch Reduce the Toxicity of dl Ser ne in Rats Proc. Soc Exper Biol & Med **57** 241 1944

56 Beve dg J M R. Lucas C C and O G ady M K The Effect of the Nature and Level of Protein and Am no Ac d Intake on the Accumulation of Fat in the Liver J B ol Ch m **154** 9 1944

57 Mitchell H H and Block R J Some Relation hips Between the Amino Ac d Cont nts of Proteins and Their Nutritive Value for the Rat J B ol Chem **163** 599 1946

of activity exhibited by the B_6 group (pyridoxine, pyridoxal and pyridoxamine) and the effectiveness of niacin, niacinamide and *nikethamide (di ethyl nicotinamide)* in pellagra

It is understood, however, that these various compounds with similar physiologic activity are active because certain essential and fundamental similarities exist in their chemical structure

Illustrative of another kind of vitamin interrelationship (many of which exist and probably more will be discovered) is the observation[59] that the utilization of tocopherols in patients suffering from muscle dystrophy was enhanced by the simultaneous injection of inositol It has been suggested that tocopherol forms a condensation product with inositol in the gastrointestinal tract and that the inherent defect in muscular dystrophy is in a deficiency of this condensation product

Other work with alpha tocopherol[60] indicates that it improves the effectiveness of suboptimal quantities of linoleic acid in preventing or curing the essential fatty acid deficiency syndrome in the rat More interesting and possibly of some practical importance, is the recent observation[61] that dietary supplementation with alpha tocopherol favorably influences milk fat concentration and total "4 per cent milk" production in the dairy cow although simultaneous use of vitamin A supplementation negates this effect of tocopherol Vitamin A supplementation alone increased the vitamin A content of the milk at the partial expense of the carotene content," but the combined supplementation of vitamins E and A "allowed the A content of the milk to rise without a pronounced fall of carotene "

Another practical relationship of vitamins is demonstrated in the finding that although cattle are able to synthesize vitamin C to meet their requirements, the amount of synthesis is greatly reduced in vitamin A deficiency In such cases the injection of vitamin C has had a beneficial effect on sterility

59 Milhorat A T and Bartels W E The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy Science **101** 93 1945

60 Howe E L and Harris P L Covitamin Studies V The Interrelation of Alpha Tocopherol and Essential Unsaturated Fatty Acids J Nutrition **31**: 699 1946

61 Harris P L Swanson W J and Hickman K C D Covitamin Studies VI Effect of Tocopherol Supplementation on the Output of Vitamin A Carotene and Fat by Dairy Cows J Nutrition **33** 411 1947

Turning to the B vitamins it has been shown in rats[62] that thiamine and pantothenic acid influence the mobilization of riboflavin in the liver and during the mobilization a portion of the transported riboflavin is excreted in the urine.

It has also been observed that on diets which contain insoluble sulfonamides the pantothenic acid utilization, as reflected by increased concentration of this vitamin in the liver of pantothenic acid deficient rats, is favorably influenced by the inclusion of biotin and folic acid in the ration.[63]

Folic acid also seems to play an important role[64] in improving the absorption of vitamin A and carotene in sprue patients. This action is probably due to the influence of folic acid in favoring a normal functioning of the gastrointestinal tract.

The foregoing examples are indications only of the multiplicity of complex relationships which may exist between vitamins and between vitamins and the other nutrients. The mechanisms involved in the many relationships can be clarified only by intensive research.

In a consideration of the effect of diet on the requirement of specific nutrients one must also consider factors which influence availability of vitamins. To illustrate this type of imbalance, it has been shown for example that certain fish products which are consumed in the raw state by man contain the enzyme thiaminase, which may appreciably destroy thiamine in the gastrointestinal tract.[65] This type of action is distinguished from the earlier mentioned "toxicants" and "inhibitors" in that here a substance is present in food that destroys another substance that is required by the host although the destructive agent is not harmful to the host directly. Obviously, reason must be exercised in estimating the practical significance of such an observation, but the

62 Supplee, G. C., Jensen, O. G., Bender, R. C., and Kahlenberg, O. J.: Factors Affecting the Riboflavin Content of the Liver. J. Biol. Chem. 144: 9 194

63 Wright, L. D., and Welch, A. D.: "Folic Acid," Biotin and Pantothenic Acid Deficiency and the Liver Storage of Various Vitamins in Rats Fed Succinylsulfathiazole in Highly Purified Rations, J. Nutrition 27: 55, 1944.

64 Darby, W. J., Kaser, M. M., and Jones, E.: The Influence of Pteroylglutamic Acid (a Member of the Vitamin M Group) on the Absorption of Vitamin A and Carotene by Patients with Sprue, J. Nutrition 33: 43, 1947.

65 Melnick, D., Hochberg, M., and Oser, B. L.: Physiological Availability of the Vitamins. II. The Effect of Dietary Thiaminase in Fish Products. J. Nutrition 30: 81, 1945.

of activity exhibited by the B_6 group (pyridoxine, pyridoxal and pyridoxamine) and the effectiveness of niacin niacinamide and nikethamide (di ethyl nicotinamide) in pellagra

It is understood, however, that these various compounds with similar physiologic activity are active because certain essential and fundamental similarities exist in their chemical structure

Illustrative of another kind of vitamin interrelationship (many of which exist and probably more will be discovered) is the observation[59] that the utilization of tocopherols in patients suffering from muscle dystrophy was enhanced by the simultaneous injection of inositol It has been suggested that tocopherol forms a condensation product with inositol in the gastrointestinal tract and that the inherent defect in muscular dystrophy is in a deficiency of this condensation product.

Other work with alpha tocopherol[60] indicates that it improves the effectiveness of suboptimal quantities of linoleic acid in preventing or curing the essential fatty acid deficiency syndrome in the rat More interesting and possibly of some practical importance is the recent observation[61] that dietary supplementation with alpha tocopherol favorably influences milk fat concentration and total 4 per cent milk' production in the dairy cow although simultaneous use of vitamin A supplementation negates this effect of tocopherol Vitamin A supplementation alone increased the vitamin A content of the milk 'at the partial expense of the carotene content," but the combined supplementation of vitamins E and A 'allowed the A content of the milk to rise without a pronounced fall of carotene"

Another practical relationship of vitamins is demonstrated in the finding that, although cattle are able to synthesize vitamin C to meet their requirements, the amount of synthesis is greatly reduced in vitamin A deficiency In such cases the injection of vitamin C has had a beneficial effect on sterility

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59 Milhorat A T and Bartels W E The Defect in Utilization of Tocopherol in Progressive Muscular Dystrophy Science **101**: 93 1945

60 Howe E L and Harris P L Covitamin Studies V The Interrelation of Alpha Tocopherol and Essential Unsaturated Fatty Acids *J Nutrition* **31**: 699 1946

61 Harris P L Swanson W J and Hickman K C. D Covitamin Studies VI *Effect of Tocopherol Supplementation on the Output of Vitamin A* Carotene and Fat by Dairy Cows J Nutrition **33** 411 1947

CHAPTER XIX

CALORIC UNDERNUTRITION AND STARVATION, WITH NOTES ON PROTEIN DEFICIENCY

ANCEL KEYS

1 INTRODUCTION

Justifiable enthusiasm about discoveries of specific nutrients and their metabolic consequence has distracted attention from the oldest problem in nutrition—simple caloric inadequacy General undernutrition with or without major deficiencies of individual nutrients, has always been widespread in the world at large, the tragedy of famine periodically emphasizes how slender is the margin of safety In the United States and Canada food production has been so abundant for many years that the direct impact of famine is unknown the *consequences of food shortages elsewhere however,* increasingly demand attention and effort here Moreover the importance of secondary undernutrition in disease is beginning to be realized.

Caloric undernutrition has been generally assumed to involve a parallel protein deficiency in most cases In Asia the area of most frequently recurring famine the diet is low in protein in the best of times Any food shortage quickly reduces such sources of proteins as are usually available and subsistence depends almost entirely on rice tapioca and other foods which contain little protein In Europe the protein in the typical famine diet is almost all of vegetable origin In any case the severely undernourished person is necessarily in a state of negative nitrogen balance so there is at least some of the effect of a protein deficiency The present discussion includes some remarks on protein deficiency (sections 7 8 and 9)

The present review is mainly an abstract of parts of a book, "The Biology of Human Starvation which *will be published by the University* of Minnesota Press in 1948 The greatest single source of data is the Minnesota experiment (1944-1946) Both book and experiment are the joint works of Dr Ancel Keys and Dr Josef Brozek Austin Henschel Olaf Mickelsen and Henry Longstreet Taylor with assistance on various phases by Miss Angie Mae Sturgeon and Drs Samuel Wells and Ernst Simonson.

fact that this condition does exist is worthy of consider ation

Another of the important factors that affect the physi ologic availability of a vitamin is apparent from the finding that of the thiamine present in live compressed yeast only a small portion is actually available to the host[66]

That there are many other extrinsic factors which may favorably or adversely affect the animal's require ment for nutritive factors is clear when one considers the general differences between species and the strain variations within species To cite such a species varia tion, one may point to the important difference between the rat and the chick in regard to their respective abilities to synthesize choline, the rat having a much more efficient mechanism for this synthesis than the chick Of course the chick's requirement for the "micronutrients in general seems to be much more critical than the rat's This holds true also for the guinea pig Strain variations in certain vitamin require ments are evident in at least the rat and the mouse

The influence of the interrelationship between hor mones and dietary constituents is certainly evident, and this whole field of investigation is advancing with great rapidity

Although the factors involved in determining what kind and how much of a particular nutrient is required for every norm il physiologic function through the entire life cycle of the organism are complex, it must be remembered that what has so far been learned about nutrient requirements still serves as a useful and prac tical tool which may be further used in elucidating some of the more complex problems

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66 Parsons H T W lliamson A and Johnson M L The Avail ability of Vitamins from Yeast I The Absorption of Thiamine by Human Subjects from Various Types of Bakers Yeast J Nutrition **29**: 373 1945

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Practical questions about general undernutrition raised by World War II clearly revealed the undeveloped state of this area in the science of nutrition Generalities about metabolic balance, normal weight for height, and optimal food intakes are of small help in evaluating *the actual degree of caloric inadequacy, in* predicting the consequences of a specific dietary level and in planning and operating programs of relief and rehabilitation This is a field in which the contribution of animal experimentation is necessarily small, quantitative *translation* from animal to man is dubious at best and impossible in terms of behavior, intellective functions, work performance and many details which have great medical and social significance The residue of useful data on man himself is surprisingly meager but has been greatly augmented in the past few years

2 SOURCE OF INFORMATION

Limitations of animal experiments have been mentioned, besides the interpretive difficulty the actual *evidence from studies on animals is not great* On man there is a plethora of general impressions and observations from famine areas, besides frequent deficiencies in technical measurement these reports usually provide only a description of the famine victims without *information about their prestarvation characteristics or* satisfactory details as to the dietary intakes which produced their present condition The same strictures may be made about the clinical literature on cachexia From a vast literature however many common points emerge for the most part these can only be incorporated, without specific citation in the present summary

Studies on a few fasting persons constitute the classic literature cited under 'starvation' in the textbooks Acute experiments with no food at all are of great interest but they have only relatively remote bearing on the problems of chronic undernutrition and the real *conditions of famine Another question* is whether the professional fasters and fanatics who have been studied are reasonable representatives of the general population

There have been two major experiments on prolonged undernutrition in man The Carnegie Institute experi*ment*[1] provided much information from a group of

1 Benedict F G Miles W R Roth P and Smith, H M Human Vitality and Efficiency Under *Prolonged Restricted Diet* Publication 280 Carnegie Institution of Washington 1919

young men who voluntarily submitted to underfeeding for several months, the degree of semistarvation was small, as indicated by weight losses of only the order of 10 per cent In the Minnesota experiment 32 young men lost an average of 24 per cent of their body weight in six months, the total period of study lasted almost two years[2]

There are no recent full-dress reviews of undernutrition and starvation but several older works are still of great value Porter[3] for a first hand account with many autopsies, of famine in India, Lusk[4] for the metabolic problems Morgulis[5] for a discussion from the point of view of the biologist and Jackson[6] for an exhaustive treatment of morphologic aspects Several recent papers provide good general pictures Leyton[7] reported observations in a prisoner of war camp where there were some elements of scientific control Data on weight changes and mortality of internees in France are valuable[8] Summaries of data on occidental persons starved in Japanese camps are available[9] Useful vital statistics and estimates of dietary intakes in periods of famine are provided for Holland[10] and for Greece[11] Data from the siege of Leningrad are interesting[12]

3 EUROPEAN AND ASIATIC FAMINE

The details of the effects of caloric undernutrition are modified by many factors including particularly the previous state of nutrition the character of the inade-

2. Keys, A Human Starvation and Its Consequences, J Am. Dietet. 22:587 587 1946.

3 Porter A. The Diseases of the Madras Famine of 1877 78 Madras Government Press, 1889

4 Lusk G The Physiological Effects of Undernutrition, Physiol Rev 1:5 3-552 1921 The Elements of the Science of Nutrition, ed. 4 Philadelphia W B Saunders Company 19 8 pp 3-117

5 Morgulis, S Fasting and Undernutrition, New York, E. P Dutton & Co Inc, 19 3

6. Jackson, C M The Effects of Inanition and Malnutrition upon Growth and Structure Philadelphia, P Blakiston's Son & Co 19 3

7 Leyton G B Effects of Slow Starvation Lancet 2: [illegible] 1946

8 Zimmer R Weill, J and Dubois, M The Nutritional Situation in the Camps of the Unoccupied Zone of France in 1941 and 1942 and Its Consequences, New England J Med. 230:[illegible] 1944

9 (a) Butler A. M Ruffin, J M, Sniffen, M M., and Wickson M E. The Nutritional Status of Civilians Rescued from Japanese Prison Camps, New England J Med. 233:639-65 , 1945 (b) Morgan, H J Wright, I S, and Van Ravenswaay, A Health of Repatriated Prisoners of War from the Far East, J A. M A. 130:[illegible] (April 13) 1946

10 Dols M J L and van Arcken, D J A. M Food Supply and Nutrition in the Netherlands During and Immediately After World War II, Milbank Mem Fund Quart. 24:319-358, 1946.

11 Valaoras, V G. Some Effects of Famine on the Population of Greece Milbank Mem Fund Quart 24: 15-[illegible] 1946

12 Brozek, J Wells, S. and Keys, A Medical Aspects of Semistarvation in Leningrad Siege 1941 1942 Am. Rev Soviet Med. 4: [illegible]66, 1946.

quate diet and the presence of intercurrent disease In spite of individual and local variations, certain patterns seem to be characteristic of European countries on the one hand and Southeastern Asia on the other

In the European countries, especially the northern and central regions, food shortages generally result in a diet dominated by whole or undermilled grains (mainly wheat), potatoes, turnips, cabbages and garden vegetables The result frequently is a diet which is surprisingly good, qualitatively, and deficiencies in vitamins and minerals may not be prominent The protein content is not vanishingly small and ordinarily comprises something like 10 per cent of the calories

The diet in Asiatic famine tends to depend on starchy and fibrous foods, which are often exceedingly poor sources of proteins, vitamins and some minerals The *common frequency of endemic infections and* infestations in Asia is exaggerated under famine conditions The combinations of these debilitating conditions are endless but those which most frequently modify the picture of simple caloric deficiency are hypoproteinemia anemia, dysentery and deficiencies of some of the vitamins Famine in Asia is attended by more severe edema and anemia and more frequent neuropathic conditions than in Europe The present review cannot treat of these complications, it deals primarily with the simpler European type of undernutrition

4 THE INCIDENCE OF GENERAL UNDERNUTRITION

A large incidence of general undernutrition seems to be an inevitable companion of national poverty and this is chronically the state of affairs in most of Asia and large sections of Africa Southeastern Europe Central and South America Until recently general undernutrition was frequently the lot of the underprivileged or economically unfortunate classes everywhere, crop failures or economic depression quickly resulted in semistarvation for the poor In the United States this situation, never very pronounced seems to have disappeared *In the great depression beginning in 1929* there was little caloric inadequacy and practically no starvation In this country severe general undernutrition because of inability to obtain food does not exist except by peculiar accident for isolated persons there is no reason to believe that this situation will change

This does not mean that there is no general undernutrition in the United States. There are recluses, invalids, children and aged persons who are unable or unwilling to disclose their want and who may be missed by the proper governmental or charitable organization. Probably far more numerous are the persons who are generally undernourished because of the presence of disease. Anorexia of some degree is undoubtedly far more common than indicated by the rare cases diagnosed as anorexia nervosa or Simmonds disease (hypopituitary cachexia). Undernutrition is prominent in the majority of patients with advanced neoplasms. Temporary undernutrition results from most severe infectious diseases and from major injuries and surgical operations.

The question of the incidence of caloric undernutrition in the general population has been raised by the results of some surveys of dietary intake. On the basis of one or another caloric yardstick, termed proper, ideal, adequate, recommended, optimal or required, comparisons are made with the estimated actual intake; if the latter value is less than the theoretic standard the case is labeled caloric insufficiency. Thus Wiehl[13] studied the diets of 1,080 aircraft workers and concluded that "the evidence is strong that a considerable number of these men were below a consumption level believed to be adequate." Further this author commented on dietary surveys in Toronto, Ontario, and Halifax, Nova Scotia, Canada, to conclude that "it is not unusual for wage earners to eat a diet with less energy than is deemed desirable."[14] The absurdity of conclusions derived from this approach is revealed by data on high school pupils.[15] More than half (55.3 per cent) of these pupils were judged to be calorically undernourished, but analysis of the physical examination data shows that of these undernourished children only 11.1 per cent were underweight while 47.7 per cent of them were overweight by 7.5 per cent or more.[16]

13. Wiehl, D. G.: Nutritional Status of Aircraft Workers in Southern California. I. Diets of a Group of Aircraft Workers in South California, Milbank Mem. Fund Quart. 20:3[illegible]9-366, 194[illegible].
14. Wiehl,[13] p. 361.
15. Wiehl, D. G.: Medical Evaluation of Nutritional Status. XV. Clinical Findings of High School Students in New York City, Milbank Mem. Fund Quart. 22:[illegible], 1944.
16. Keys, A.: The Refinement of Metabolic Calculations for Nutritional Purposes and the Problem of "Availability," editorial, J. Nutrition, 29:81-84, 1945.

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13 Wiehl D G Nutritional Status of Aircraft Workers in Southern California I Diets of a Group of Aircraft Workers in South California Milbank Mem Fund Quart. **20** 329 366 1942

14 Wiehl[13] p 361

15 Wiehl D G Medical Evaluation of Nutritional Status XV Caloric Intake of High School *Students in New York City* Milbank Mem Fund Quart **22** 5-40 1944

16 Keys A The Refinement of Metabolic Calculations for Nutritional Purposes and the Problem of Availability editorial J Nutrition **29**: 81 84 1945

5 CALORIC REQUIREMENTS AND RECOMMENDATIONS

The term *caloric requirements* is widely used, but so far has escaped precise definition nor will this be attempted here With any reasonable definition the requirement will be dependent on body size, age, sex climate occupation, personal habits, previous state of nutrition and perhaps race

It is not possible to draw a fine line between caloric adequacy and general undernutrition, least of all by using the caloric intake alone as the criterion In a given person caloric balance can be maintained over a rather wide range of body weight and caloric intake and it is not now possible to conclude whether, in the long run, the optimal condition would be toward the upper or lower end of a range amounting to perhaps 10 per cent or more of the average body weight Changes in body weights are a different matter and a person not previously obese who loses 10 per cent or more in weight and continues to lose weight is clearly calorically deficient, roughly the same criterion may be applied to the averages for populations

Various authorities (e g, the League of Nations and the National Research Council) have made recommendations regarding caloric intake These are useful in comparing populations and in planning food production such validity as they have is that of broad averages and their application to individuals is unwarranted By and large, the caloric recommendations of the League of Nations and of the National Research Council may be rather higher than optimal Slight to moderate decreases in per capita consumption below these recommendations in England and Switzerland in World War II and after were associated with evidences of better health The role of changes in quality of food in these results is obscure but certainly no adverse effect can be claimed from the caloric reductions Fleisch[17] concluded that instead of a required average of 2 400 Calories for sedentary adults the experience of World War II showed an average intake of 2,160 Calories to be sufficient and even beneficial in Switzerland In the United States careful studies on caloric

17 Fleisch A Ernahrungsprobleme in Mangelz ten D e schwe er ische Kriegsernahrung 1939 1946 Basel B nno Schwabe & Co 1947

intake reveal surprisingly low values in some instances where there is no clinical indication of inadequacy[18]

6. FASTING AND ACUTE STARVATION

Both fasting (total abstinence from food) and prolonged undernutrition result in many similar effects such as bradycardia, lowered metabolic rate, hypotension and weakness But there are also obvious important differences a few of these may be noted simply to emphasize the point that results in fasting experiments cannot be applied in any detail to problems of chronic undernutrition Prolonged fasting has its intrinsic scientific interest but it is rarely encountered in nature

All reports on fasting are in agreement that the sense of hunger quickly disappears as the fast is continued *If the subject is sedentary hunger is seldom disturbing* after the third day and is usually entirely absent in a week This loss of hunger is much accelerated by physical work In experiments in the Laboratory of Physiological Hygiene fasting young men doing hard physical work lost the sensation of hunger in twenty four hours and incipient nausea with the attendant revulsion to food, was troublesome on the second or third days This is in sharp contrast with undernutrition in which the sense of hunger progressively increases until it occupies a major part of the consciousness Only near the termination with death from starvation does the condition change to resemble that in total fasting Besides such differences in physical sensation there are decided tendencies to differences in emotional state Depression and apathy are almost universally observed in persons with severe undernutrition but in sedentary fasting euphoria and states of excitement are not uncommon

It may be presumed that fasting is a greater certainly a more abrupt emergency and therefore a stronger stimulus to mobilize defense mechanisms in the body This together with the simple factor of time may account for some differences in the blood chemistry compared with that in chronic undernutrition The concentration of both erythrocytes and leukocytes in the blood of fasting persons tends to remain within relatively normal limits, though subject to variations from time to time Simple undernutrition however, tends to produce a leukopenia and a progressive anemia

18 Winters J C and Leslie, R E. A Study of the Diet of Twenty Women in a Moderate-Income Group J Nutrition 27 185 192 1944

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17 Fleisch A Ernahrungsprobleme in Mangelzeiten Die schweizerische *Kriegsernahrung 1939 1946 Basel Benno Schwabe & Co 1947*

As in the case of calories, the concept of protein deficiency also involves consideration of protein requirements, presumably deficiency exists when requirements are not met The situation is more complicated with proteins than with calories because there are several modifying factors On the other hand the criteria for establishing protein requirements are, at first glance simpler and more objective

In the growing animal it is customary to consider the least amount of protein which will allow the maximal rate of growth to be the requirement Clearly this is the requirement for maximal growth but for what else? Whether this level is optimal is an abstruse question which is seldom asked and which, actually may be unanswerable without more precise definition Optimal for what? In the case of animals the only values which are readily examined are size and appearance, physical health—meaning merely the absence of disease and defects—and longevity The latter is infrequently considered perhaps because the small evidence available points to an inverse correlation between rate of growth and eventual longevity Numerous factors of great human value which may be affected by the level of protein nutrition are almost never considered, let alone evaluated

In the adult the usual criterion for the protein requirement is the least intake level which will maintain nitrogen balance In practice the method is more troublesome than in theory because of the tendency to spontaneous variation and the difficulty of obtaining exact balance The expedient of measuring nitrogen excretion in fasting or on a protein free diet is used to get a minimal estimate of the endogenous protein destruction but this does not tell how much intake of a particular protein or protein mixture will result in nitrogen balance

Labile protein reserves (depot nitrogen) in the body are generally considered to be very small, and a sizable negative nitrogen balance for more than a day or two is taken to mean tissue depletion or destruction But there are situations in which a negative nitrogen balance seems to be physiologic or at least difficult to avoid and perhaps harmless

Perhaps the most striking differences between total and partial inanition are related to the differences in carbohydrate metabolism Only a small supply of exogenous carbohydrate (which may be supplied also from exogenous protein) suffices to prevent ketosis The amount required for this—of the order of 600 Calories per day—is usually obtained even in the worst conditions of famine In any event, ketosis and keto nuria do not ordinarily appear in chronic undernutrition but pronounced ketosis develops in a few days of fast ing Associated with this difference in respect to ketosis are differences in the respiratory quotient in acid base balance and in the blood sugar level

In the studies in the Laboratory of Physiological Hygiene there were observed interesting differences in the relative resistance of various functions to fasting on the one hand and to prolonged undernutrition on the other For example strength as measured in single maximal exertions is relatively resistant to fasting but is definitely reduced by prolonged underfeeding In contrast, the coordination of movements is more strik ing, reduced by fasting than by semistarvation

7 PROTEIN DEFICIENCY AND REQUIREMENTS

Pure protein deficiency with adequate calories and vitamins is probably seldom encountered in nature and little is known about it in man That it retards or reverses growth and leads to hypoproteinemia and anemia is clear In Asia it contributes to the picture of famine edema and probably frequently complicates the decision as to whether there is a major deficiency of calories or thiamine Protein deficiency will be con sidered here mainly as it may be associated with gen eral undernutrition or may be confused with it

Where caloric inadequacy exists the importance of the protein intake is dubious because the protein tends to be used as fuel in place of fat and carbohydrate and thereby is deprived of its ordinary important function At exceedingly low levels of caloric intake—below 1 000 Calories daily for an adult—the substitution of protein for carbohydrate in the diet has practically no effect on the balance and the net nitrogen loss from the body continues At higher but still inadequate levels of caloric intake it may be that dietary protein may spare some nitrogen loss but the evidence is not fully satis- factory

kilogram of body weight for adults But in studies on young men doing hard work in the open no advantage was found for intakes greater than about two thirds this amount even when much of the protein was from vegetable sources [0] This tends to be in agreement with recent careful studies on nitrogen balance in which it was concluded that the National Research Council recommendation for a 70 Kg man could be reduced to 50 Gm and still provide approximately 30 per cent margin above requirements [21]

The conclusions indicated in the preceding paragraph will be challenged by those who believe that neither crude nitrogen balance nor performance in normal health tell the whole story Large excesses of protein intake have been suggested to be advantageous in building up reserves or antibodies which may be called on to meet the emergencies of disease or injury The evidence is still controversial except in the case of persons who have been in negative nitrogen balance and in whom a period of positive balance may be restorative But elevated protein intakes are not clearly detrimental though they are expensive and will undoubtedly be recommended by many nutritionists to be "on the safe side"

9 PROTEIN QUALITY

Long ago animal feeding experiments with different individual proteins demonstrated differences in quality the protein requirement was different for the several proteins Some of the vegetable proteins were notably inferior to the animal proteins and it became customary to believe that a considerably greater intake of vegetable proteins was required as compared to animal proteins Some of this difference could be traced to differences in digestibility and absorption but more important discrepancies were related to metabolic utilization It is now agreed that the last is dependent on the amino acid composition of the proteins Inadequacy of one essential amino acid limits the synthesis of the tissue proteins which must contain it and thereby leaves excesses of the other amino acids which are then use less for this purpose Accordingly general protein deficiency *may result from lack* of a single amino acid

0 Da ling R C Johnson R. E P tts G C Consolazio F C and Rob nson P F Effects of Variations in D tary Prote n on the Physical Well B ing of Men Doing Manual Wo k J Nutrition 28: 273 81 1944

21 H gsted D M Tsongas A G Abbott D B and Star F J Prote n Requirements of Adults J Lab & Clin. Med 31: 261 284 1946

8 NITROGEN BALANCE AND PHYSICAL ACTIVITY

Protein catabolism is not increased in muscular exer cise, the protein requirement is not altered by partici pation of protein in the direct energetics of physical activity This does not mean that the nitrogen balance and requirement are independent of the activity in the long run

In bed rest, which is the most frequently prescribed therapy in all forms of disease and injury the nitrogen balance quickly becomes negative on any ordinary diet and this occurs even in the absence of disease or injury on the resumption of normal activity the nitrogen bal ance of the patient becomes positive This phenomenon would seem to be a kind of disuse atrophy, probably most of the nitrogen lost comes from muscle cytoplasm and there may be no actual cellular destruction at least at first Similarly chronic intensification of activity and muscular exercise calls for increased sarcoplasm and therefore nitrogen retention (exercise hypertro phy) It is puzzling however to find that even in bed rest and in the presence of situations that involve destruction of tissue there may be a positive nitrogen balance if the protein intake is forced to extremely high levels [19] Decreases in hemoglobin and plasma protein may occur in infections even when nitrogen retention is good [19a]

Somewhat similar difficulties arise from the fact that a definitely positive nitrogen balance in adults may be induced by some hormones notably testosterone pro pionate It is difficult to avoid the conclusion that the old discussion of protein reserves must be reopened Since no specific reservoir of labile protein can be found it may be suspected that the tissue cells in gen eral have some nitrogen reserve and storage capacity

In any case the concept of protein requirements seems less simple and precise than might have been hoped The optimal protein intake may be something else again but there is little evidence as to quantitative relationships The recommendations of many authori ties including the League of Nations and the National Research Council tend to fix on 1 Gm of protein per

19 (*a*) Sp nse H Y Evans E I and Forbes J C The Influence of Special High Protein Diet on Protein Regeneration in the Surgical Patient Ann Surg **124** 131 141 1946 (*b*) Howard J E and others Studies on Convalescence Nitrogen and Mineral Balances During Starvation and Graduated Feeding in Healthy Young Males at Bed Rest, Bull Johns Hopkins Hosp **78** 282-307 1946

allowance may be made for bodily build or type, with standards beings broken down into groups such as large frame and small frame There is no agreement as to how these body types may be properly segregated

Regardless of refinements of measurements and classification, *all these standards involve some major uncertainties* First, the designation healthy in the reference group means only the absence of obvious disease and defect, and all persons in the reference group are presumed to be equally healthy a presumption without basis and certainly false if it is admitted that health has gradations Secondly, it is assumed implicitly that the average somehow connotes the best, this is a nice *democratic arrangement but scarcely scientific*

Presumably the main concern in all examinations of height and weight is the proportion of the body represented by fat In very emaciated and in very obese persons the principal difference is in the amount of fat, and this may be roughly gauged by the gross weight Outside of these extremes however—and it is precisely with less extreme cases than the real interest lies —*the relation of fat to weight is far less exact*

The body fat may be estimated from its specific gravity taking advantage of the low density of fat [23] When this is done with a group of ordinary men, with no great extremes of emaciation or obesity there is no correlation between true fatness and the degree of overweight or underweight calculated from height-weight tables [24]

II WEIGHT LOSS IN UNDERNUTRITION

Reliable data on weight losses in famine and chronic undernutrition are remarkably few The person who is semistarved against his will almost invariably overestimates his prestarvation weight and his weight loss The same is often true of persons on reducing diets

As noted previously true ideal weights are not known and it is not possible to define precisely the level at which weight loss or departure from standard average

23 Behnke A R., Jr Feen B G and Welham W C. The Specific Gravity of Healthy Men Body Weight Divided by Volume as an Index of Obesity J A M A **118** 495-498 (Feb 14) 1942 Rathbun E N and Pace N Studies on Body Composition I The Determination of Total Body Fat by Means of the Body Specific Gravity J Biol. Chem. **158** 667 676 1945 Morales M F Rathbun E N Smith, R E and Pace N Studies on Body Composition II Theoretical Considerations Regarding the Major Body Tissue Components with Suggestions for Application to Man ibid. **158** 677 684 1945

24 Laboratory of Physiological Hygiene University of Minnesota, unpublished studies

In actual practice, that is, under the great majority of natural conditions, the importance of protein quality is much less than previously supposed. In ordinary diets, even of the vegetarian type, the protein moiety is made up of many different proteins and the chance that all of them will be low in one or more amino acids is small. On diets of limited variety, however, it is possible to have conditions like the earlier rat experiments in which substantially all the protein is supplied by a very few proteins. Such a condition may easily arise in famine areas; in such cases the provision of small amounts of food rich in the missing amino acids may be highly beneficial.

An example of unsuspected amino acid deficiency and an interrelationship with a vitamin has recently emerged in pellagra. It now appears that pellagra may result from a deficiency in either tryptophan or niacin and may be successfully treated by either the amino acid or the vitamin.[22] This means that the protein requirement may be altered by either its tryptophan content or by the amount of niacin in the diet. It is entirely possible that other similar relationships between amino acids and vitamins will be discovered. The protein requirement is certainly not an independent entity.

10 THE PROBLEM OF BODY WEIGHT AND FAT

Caloric inadequacy produces a weight loss or a low level of weight for height. In practice dependence in diagnosis is usually on the height weight relationship; this means comparison with some set of standards. It is essential to recognize the derivation and limitations of such standards. Since there are as yet neither theoretic nor experimental bases for establishing ideal or optimal relationships between height and weight, recourse is had to averages of supposedly healthy groups which are taken as the standards. The body weight of a given person is then compared with the average of a group of healthy persons of the same sex, age and height. The difference between the individual and the group average is then expressed as pounds overweight or underweight. As an added refinement

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22 Krehl, W. A., Teply, L. J., Sarma, P. S., and Elvehjem, C. A.: Growth Retarding Effect of Corn in Nicotinic Acid Low Rations and Its Counteraction by Tryptophane, Science **101**: 489-490, 1945. Salmon, W. D.: Relation of Corn Products to the Requirement of the Rat for Dietary Nicotinic Acid, J. Nutrition **33**: 169-175, 1947.

Droese[25] pointed out the confusion in the literature on the classification of the osteopathies associated with undernutrition but believed that hunger osteoporosis can be distinguished from hunger osteomalacia and late rickets At the end of World War I a wide variety of osseous disorders were described from Central and Eastern Europe,[26] including delayed ossification in young women[26a] and multiple spontaneous fractures[27] *All ages were represented but the incidence was perhaps highest in elderly women*

In World War II osteopathies again were noted in Europe, the most frequently observed form being that in which there are areas of translucency in the cortex of the long bones and spontaneous fractures at points of mechanical strain[28] Pompen and associates[28b] described 24 cases of what they called hunger oste opathy ' They stated that in all cases the diet had been deficient in calcium phosphorus protein and vitamin D, and many of the patients had been indoors for long periods Though undernourished these patients were not really starved This situation is radically different from that of the American prisoners of war in Japanese prison camps who showed roentgenologic evidence of osteoporosis on repatriation these persons had ample exposure to the sun and frequently ate ground fish bones in prison[29] Such evidence does not support a belief that either calcium or vitamin D deficiency is essential to the development of hunger osteopathy

In the Minnesota experiment bone density was studied by Dr Pauline Berry Mack with elaborate quantitative methods developed at Pennsylvania State College Evidence of any abnormality in bone density was not seen It seems probable that hunger osteopa thies tend to develop only when the undernutrition is prolonged (for a year or more) and even then there

25 Droese W Be trag zur Frage der senilen Osteomalaz e und der Hungerost path Mun h n med Wschnschr **85** 1199 1202 1938

26 (*a*) Boehme A G hauft auftret nde Knochenerkrankungen infolge von Unternahrung Deuts he med Wchnschr **45** 1160 1162 1919 (*b*) Staun g K Ro ntgenbefunde be alimentarer Skelettschad gung W n. Kl n Wchnschr **32** 712 713 1919

27 Alwens U be die Bez hungen der Unternah ung ür Osteo p r se und Ost omalazie Munchen *med Wchnschr* **66** *1071 1075* 1919 Boehme[26]

28 (*a*) Burger G C E Sandstead H R. and Drummond J Starvation in Western Holland Lan et **2** 282 83 1945 (*b*) Pompen A W M La Chappelle E H G oen J and Merex K P M Hunger Osteomalacie in Nederland Amsterdam Wetenchappel jke U tgever j 1946

29 H bbs R E. Personal communication to the author

becomes important Probably deviations of less than 10 per cent below standard average weight for height are of small moment per se. On the other hand a sudden weight loss of as much as 5 per cent may be significant Weight losses of 10 per cent or more that are brought about in a few months in persons not previously obese involve definite impairment in endurance and working capacity and are associated with adverse changes in personality and emotional status

In previously healthy young adults weight losses up to about 30 per cent can be tolerated with every prospect of eventual full return to normal with proper rehabilitation care The lethal level is generally around a 40 per cent weight loss though instances of losses of 50 per cent of weight with recovery have been recorded In severe semistarvation the true weight loss may be difficult to estimate because of the presence of edema the foregoing figures are for gross weight including the ordinary amount of edema When there are exceptionally pronounced edema and ascites the lethal point may be reached with weight losses of only 20 to 30 per cent

The rate at which weight is lost in undernutrition is of consequence In general it seems that the more rapid the weight loss the more serious is the disability at equal total weight losses This is a point of both theoretic and practical interest which deserves special study Allied to this problem is that of adaptive and compensatory phenomena in persons who are habitually underweight in comparison with ordinary standards

12 MORPHOLOGY BONES AND TEETH

The bony structures of the body are relatively resistant to caloric undernutrition No adverse effect on the formed teeth has been objectively demonstrated in either acute or chronic starvation The bones however are not totally immune from change. Hunger or famine osteopathies have been reported many times in both European and Asiatic persons Whether the affected individuals are peculiar in one or another respect or may only exhibit a more advanced state of a general tendency is not clear It is probable that mild degrees of decalcification or other osteopathies are seldom recognized

In the Minnesota experiment the major axis of the heart in the standing position was on the average, 4.4 degrees more vertical in starvation than in the control period

14 MORPHOLOGY BRAIN AND NERVOUS TISSUE

It has long been taught that the brain and the heart are somewhat "protected" in starvation so that they do not shrink and waste as do the other soft tissues of the body In the case of the heart as has been noted this view is in error But all evidence is in agreement that the brain and nervous tissue generally loses little weight even in severe starvation This does not necessarily mean however that these tissues are really unaffected by undernutrition Histologic examination reveals atrophy cloudy swelling chromatolysis and a variety of degenerative changes in the cells[32] The explanation of the apparent paradox may be suggested by the general agreement that vacuoles and evidences of edema appear in the nervous tissue Presumably the weight changes are limited because the gross structure is preserved with replacement of cytoplasm or even of cells by water The changes in the spinal cord are similar to those in the brain and may be even more pronounced in the anterior horn cells[33] Nor are the peripheral nerves immune to the effects of starvation though the medullated fibers are only slightly affected morphologically[6]

15 SKIN HAIR AND EYES

Caloric deficiency of more than slight degree tends to produce characteristic changes in the skin and hair but these are not specifically pathognomonic The skin becomes thin dry scaly inelastic, pallid and grayish It is cold and "dead" to the touch and tends to slight cyanosis in cold weather The appearance suggests old age Besides these changes which are generally seen and were striking in the men in the Minnesota experiment, there are other changes which appear with less regularity

A substantial proportion of persons subsisting on a European type of famine diet exhibit rough gooseflesh-like areas of skin most often on the extensor surfaces of the thighs and upper arms The condition resembles the follicular hyperkeratitis and folliculosis sometimes

32 Jackson, p 181
33 Jackson, p. 195

must be other factors operative because the incidence never seems to be exceedingly high in famine populations

13 MORPHOLOGY MUSCULAR TISSUES

Muscular wasting is always a prominent feature of severe undernutrition Experimental studies on animals indicate that, in general the percentage weight loss of the voluntary muscles is somewhat greater than percentage weight loss of the entire body Most of this wasting seems to be a result of shrinkage of the individual muscle fibers but in late stages actual destruction of the cells may occur (Jackson[8] page 162) Brown atrophy loss of cross striations and granular degeneration have been described as well as a reduction in the liposomes (minute fat droplets) and occasional appearance of vacuoles

Presumably moderate undernutrition only affects the mass of sarcoplasm at least for a time and full recovery on refeeding should be possible With more severe starvation where muscle cells are undergoing actual destruction it may be thought that full recovery could be brought about only by relative hypertrophy of the remaining intact muscle cells However, mitoses in skeletal muscle of adult animals have been reported during ample feeding following starvation[30]

Contrary to the textbooks heart muscle behaves much like skeletal muscle in starvation In both acute and chronic undernutrition the heart shrinks in volume and in weight the loss being nearly in proportion to the total weight loss of the body[31] In the Minnesota experiment the average gross volume of the heart at systole measured from teleroentgenkymograms decreased 17 per cent when the body weight decreased 24 per cent. Since the starved heart may well eject its blood less completely than the normal heart the actual tissue loss may be underestimated by this roentgenologic method but in animals the weight loss of the heart is generally a trifle less than proportionate to the total weight loss

The position of the heart in the chest is also changed in starvation so that ordinary linear measurements do not give an exact indication of the change in total size

30 Jackson[8] p 167

31 Keys A Henschel A and Taylor H L. The Si e and Function of the Human Heart t R st in Sem Star at on and in Subsequent Rehab l tat on Am J Phys ol. **150** 153 169 1947

ods refer only to the circulating blood Although in man the reservoirs of noncirculating blood are small it is possible that the situation may not be precisely the *same in normal and in starved persons* Moreover when starved and normal persons are compared there is the question as to how the blood volume should be expressed to allow properly for differences in gross body size

Plasma volume was estimated in 15 inmates of the Belsen concentration camp who had lost something like 30 or 35 per cent of their body weight[35] In the Minnesota experiment the plasma volume was studied sys*tematically before during and after starvation*[36] As far as they go, the Belsen data confirm the Minnesota work Before starvation the Minnesota subjects had an average plasma volume of 3 15 liters and this amounted to 45 3 ml per kilogram of body weight At the end of six months of semistarvation the absolute plasma volume had increased slightly to an average of *3 41 liters* but this *then represented 59 3 ml per kilo* gram of the total body weight

The absolute plasma volume then tends to remain constant or increases slightly in starvation The associated anemia means that the total circulating blood volume is somewhat reduced but in proportion to the body weight there is a definite blood plethora These changes are *slowly* reversed in subsequent rehabilitation, the Minnesota men were fully restored in this respect in about three months

The behavior of the blood volume in the terminal stages of the most severe starvation may be more complex Some famine victims die in obvious shock with all signs of severe dehydration the persistent diarrhea *often seen in these cases may produce dehydration* sharp reduction in blood volume and shock as in cholera

17 MORPHOLOGY BLOOD CELLS

Some degree of anemia is invariably observed in persons who have undergone prolonged *semistarvation* In Asia severe anemia is frequently seen in such persons but this is probably mainly a reflection of the effect of malaria and other blood destructive conditions

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35 Mollison P L. Observation on Cases of Starvation at Belsen Brit. J 1 4 8 1946

36 Henschel A Mickelsen O Taylor, H L. and Keys, A Plasma Volume and Thiocyanate Space in Famine and Recovery Am J Physiol 150 1 0-180 1947

associated with vitamin A deficiency The causation is puzzling because its incidence is highly variable and does not seem to be clearly related to the state of vitamin A nutrition[34] This condition did not appear in the inmates of Japanese prison camps in spite of gross dietary deficiencies[9a]

A remarkable peculiarity of the skin in starvation has escaped serious attention until recently A splotchy dirty brownish pigmentation, appearing anywhere on the body but most often seen on the face, was casually mentioned in some old reports on undernutrition but occasioned much surprise when it was frequently seen at the close of World War II[28a] Most of the Minnesota men exhibited it to some degree The mechanism of the production of this famine pigmentation is unknown, it is not related to niacin deficiency or pellagra

The hair in starvation is usually dry dull and staring There are many impressions that hair almost ceases to grow and tends to fall out but objective evidence is lacking

There is a characteristic appearance of the eyes in starved persons They look dull and dead On closer inspection it is seen that the sclera and cornea are unusually devoid of blood vessels so that the whites of the eyes resemble unglazed porcelain In the Minnesota experiment men even soap solution failed to produce reddening

16 MORPHOLOGY BLOOD VOLUME

With the exception of bone and nervous tissues, the formed tissues of the body generally are decidedly diminished in gross bulk in undernutrition In some respects it is proper to consider the blood as a tissue and its behavior in comparison with other tissues is of interest More particularly it is essential to allow for changes in the gross mass of the blood before evaluating the true meaning of changes in the concentration of the formed elements

Measurements of the blood volume in relation to the nutritional state are still few in number and some limitations in the technical methods restrict the conclusions which may be drawn from the data All present meth

34 Robinson W D Janney J H and Grande F C An Evaluation of the Nutritional Status of a Population Group in Madrid Spain During the Summer of 1941 J Nutrition 24 557 584 1942

Correcting for the change in total blood volume the decrease in total circulating leukocytes averaged 24 1 per cent

The composition of the leukocytes by types in semistarvation and in fasting has been reported many times in the older literature, but no consistent picture emerges Several workers found an apparent relative lymphocytosis[38] but this was not observed in the Minnesota experiment.

In rehabilitation following prolonged undernutrition the correction of the anemia takes place slowly even when protein and iron are supplied in abundance In the Minnesota experiment the hemoglobin concentration only recovered slightly in 12 weeks and was still appreciably below the control values at 20 weeks when the body weight had been regained 3 months later however (i e a total of 8 months after the end of semistarvation) the blood was normal

18. THE GASTROINTESTINAL TRACT

Gastrointestinal disorders are almost invariably reported from famine areas and frequently contribute greatly to the disability and death of famine victims Diarrhea and dysentery are always major factors in famine mortality in India,[39] and were prevalent in Europe in both World Wars[40] The majority of internees and prisoners of war in the Japanese camps in World War II suffered from diarrhea[9a] In such situations however there is a breakdown of sanitation or recourse to strange and peculiar materials as food or both so that it is impossible to assess the effects of undernutrition as such

Attempts to isolate specific pathogens from the stools in most of these cases have been conspicuously unsuccessful If organisms in the intestine are responsible it must be concluded that forms which normally are not pathogenic may interfere with the function of the intestine of the starving man Famine victims usually eat anything and everything they can get, and this often means the consumption of irritating indigestible and

38 Bigland A. D Oedema as a Symptom in So-Called Deficiency Diseases Lancet 1 243-47 1920 Benedict Miles, Roth and Smith.[1]
39 Aykroyd W R. Nutrition and Health Indian M. Rec. 59 113 116 1939 Porter[8]
40 Debray C Zarachovitch M Ransom B Jacquemin J Robert, G and Sparaga, M Contribution a l'etude de la pathologie des deportés, Semaine d hop de Paris 22 803-810 1946 Brozek, Wells and Keys.[32] Burger Sandstead and Drummond.[9a]

In the Minnesota experiment the diet like European famine diets, was not deficient in iron but there was a progressive moderate anemia in every man during semistarvation Beginning with an average of 15.1 ± 0.88 Gm per hundred milliliters of blood in the control period, the average value declined to 12.6 ± 0.80 Gm after 12 weeks of semistarvation (15 per cent weight loss) and to 11.7 ± 0.80 Gm at 24 weeks when the weight loss was 24 per cent[36] These changes are comparable to many observations in famine areas in Europe

In general, the erythrocyte count and the hematocrit reading change as does the hemoglobin concentration but the parallelism is not exact The red blood cells tend to become slightly larger in starvation, the anemia is of the macrocytic type In the Minnesota experiment the average volume of the red cell and the content of hemoglobin in it had increased about 7 per cent at the end of semistarvation

From the data on plasma volume the hematocrit reading and the hemoglobin concentration, the total circulating hemoglobin can be calculated In starvation this is decreased the decrease in the Minnesota experiment being almost exactly in proportion to the decrease in gross body weight[36]

The cause of the anemia in undernutrition is not clear iron deficiency is not primarily responsible Sternal marrow examinations so far have not provided the answer Increased decreased and normal degrees of erythropoiesis have been found in the marrows of anemic starving persons The possibility that excessive peripheral destruction of the red blood cells is involved is suggested by reports of hemosiderin deposits in the tissue[37]

In comparison with the rather large variability of leukocytes in normal subjects, the changes in starvation are ordinarily not dramatic A definite but moderate leukopenia is the rule except where there is intercurrent infection In the Minnesota experiment the mean leukocyte count was 6,346 per cubic millimeter in the control period and at the end of semistarvation it was 4,129, a decline of 34.9 per cent (see also Zimmer[8])

37 Lubarsch cited by Luisada A Beitrag zur Pathogenese und Therapie des Lungenodems und des Asthma cardial Arch. f exper Path u. Pharmakol 132 313-329 1928

the caloric intake is a major determinant in the caloric balance Under normal conditions the basal metabolic rate of the individual is relatively fixed and differences between persons of the same age and sex are considered to be dependent on body size and on the activity of the thyroid gland It is generally believed that habitual differences in food intake and relative obesity in normal persons have little or no effect on the basal metabolic rate Persons who are habitually thin, even to a decided degree apparently have a normal basal metabolic rate when this is expressed per unit of body surface [42]

When the food intake is sharply reduced below the habitual level for the subject the basal oxygen consumption promptly declines and this alteration tends to be progressive if the inadequate diet is continued, the absolute change is large The 32 men in the Minnesota experiment had an average basal consumption of 229 ml per minute before starvation After 12 weeks of the famine diet when the body weight had fallen 15 per cent this had decreased to 155 ml and after 24 weeks the average was 139 ml per minute, a loss of 24 per cent in body weight was associated with a *drop of 39 per cent in the basal oxygen consumption* These data, which extend and confirm earlier results, are of obvious practical significance When subsistence is maintained at a calorically deficient level the progress of the undernutrition itself progressively decreases the caloric deficit so that there is a tendency toward adaptation or compensation

The absolute changes in the basal metabolism raise questions about the mechanisms involved and the intensity and character of the metabolic processes in the metabolizing tissues These changes are not merely a reflection of changes in the body surface which would be predicted from the so called surface law In the Minnesota experiment, for example, there was an average drop of 28 per cent in the oxygen consumption per square meter of body surface Subnormal values for the basal metabolic rate expressed in units of body surface are universally found in famine areas

Analysis of these data suggests the need for renewed scrutiny of the surface law As the body shrinks in

42 Blunt, K, Nelson A, and Oleson H C The Basal Metabolism of Underweight Children J Biol. Chem 49: 247 262 1921 Strang J M, McCluggage H B and Brownlee M A Metabolism in Undernutrition Its Changes During Treatment by High Caloric Diet, Arch. Int. Med 55: 958-978 (June) 1935

spoiled foods, so that nonspecific diarrhea would not be surprising except for its severity

In the Minnesota experiment, in which strict sanitation was maintained and bad or questionable items of food were never used, diarrhea did not occur at any time though the degree of starvation was comparable to that in the field where diarrhea is so pronounced This would seem to prove that starvation alone is not causative

Extreme pathologic changes are often found in the intestinal mucosa of famine victims These changes may explain the diarrhea in a sense, but the tissue changes are probably the resultant of several factors, of which caloric undernutrition is only one. Certainly starvation produces degenerative changes in all the tissues of the gastrointestinal tract as elsewhere in the body Additional insult may then easily produce a variety of disorders An increase in peptic ulcer is commonly noted in periods of undernutrition [41]

The course of the digestion as affected by starvation is an important question in devising relief programs In the spring of 1945 it was at first thought that many famine victims in Europe would require intravenous alimentation but this proved undesirable in trials in the Netherlands and later in the Belsen concentration camp Frequent feedings of easily digested foods usually bring about rapid improvement, when this is not the case even the most careful intravenous management may be unsuccessful The critical point may be indicated by dysphagia If the patient still feels the pangs of hunger and wants to eat, even a rough and ready feeding program with plain foods will suffice, if the appetite is gone the prognosis is bad (except in anorexia nervosa)

In the Minnesota experiment there were few indications of digestive impairment and no complaints on this score Gastric acidity (fasting and after histamine) was substantially normal Gastric motility (rate of evacuation of a test meal) was slightly but consistently depressed

19 THE BASAL METABOLIC RATE

The basal metabolic rate always represents a large fraction of the total metabolism so that its relation to

41 Magee H E Application of Nutrition to Public Health Some Lessons of the War Brit M J 1:475-486 1946

tissue or per unit of body weight less fat In the latter terms the average for the men in the Minnesota experiment after 20 weeks of refeeding, when body weight had been restored, was 13 per cent above their own normal metabolic rates

20 TOTAL ENERGY METABOLISM

The total energy metabolism is made up of the basal metabolic rate the specific dynamic action (some 10 per cent of the basal metabolic rate), and the cost of muscular movement and tonus in excess of the basal state In starvation or severe undernutrition the basal metabolic rate is sharply diminished as previously noted *Presumably there is also a proportional reduction* in the specific dynamic action The other items *in the total metabolic picture are also much reduced*

The energetic efficiency of muscular activity is substantially unaltered in undernutrition except in the most extreme states where gross incoordination may interfere The energy cost per kilogrammeter of external work like walking and bicycle riding is practically unaltered This simplifies the analysis

A large part of the energy cost of muscular work is entailed by moving the body or its parts In locomotion the work done is simply proportional to the body weight It follows, then that the metabolic cost of muscular work is reduced in starvation because of the reduction in weight of the body and its movable parts *For the majority of activities the reduction in work* energy may be considered roughly proportional to the *loss in body weight*

Perhaps even more important in most natural life situations is the fact that voluntary activity is greatly diminished in severe undernutrition Energy expenditure is automatically curtailed and the starving man tends to be immobile to move slowly when movement is necessary and to assume postures which are most conservative of energy

The combined effect of all these factors is a large reduction in energy expenditure In the Minnesota experiment the daily total energy expenditure at the end of semistarvation was only about half that in the control period in spite of the fact that a fixed occupational and exercise program was maintained throughout In severe natural famine the reduction in energy expenditure may be considerably greater so that caloric balance

starvation the surface increases relative to the tissue mass so that, other things being equal, there would be a greater heat loss and a lower point of temperature equilibrium The lowered body temperature in turn would retard the enzymatic processes which constitute the metabolism Although such a chain of events undoubtedly operates, it is not possible to explain the total metabolic alterations on this basis The decline in body temperature is exceedingly small, in the Minnesota experiment it fell less than 1 degree (F) in 24 weeks As a matter of fact, the theory of a heat exchange basis for the surface law is no longer seriously entertained Changes in peripheral blood circulation readily control the body temperature in the face of great changes in heat production and external temperature

An important problem is the behavior of the metabolic rate per unit of metabolizing tissue A first approximation is obtained by expressing the metabolic rate in relation to gross body weight In the Minnesota experiment the basal oxygen consumption per kilogram of body weight declined 15 per cent in semistarvation But the gross body weight is not necessarily a reliable index of metabolizing tissue Fat bone mineral and extracellular water clearly have little or no metabolic activity In starvation the proportional composition of the body is changed there being a relative reduction in fat and relative increases in bone mineral and extracellular water When allowance is made for these differences which is possible with the Minnesota data the apparent alteration in metabolic intensity is reduced but the values are still about 10 per cent below the prestarvation control In other words prolonged severe undernutrition produces a small but seemingly significant drop in the basal metabolic rate per unit weight of active tissue (body weight less weights of fat bone mineral and extracellular water)

In rehabilitation following undernutrition the basal metabolic rate rises more or less parallel to the dietary intake and the gain in body weight Before body weight is fully restored however and for some weeks or months thereafter the basal metabolic rate surpasses the value which was characteristic of the subject in the prestarvation state This is particularly clear when the basal metabolic rate is expressed per unit of active

in both absolute and relative terms The electrocardiogram in a state of severe undernutrition shows peculiarities *in almost every item of measurement*[43b] but the amplitude changes are most striking The voltages of all deflections are reduced, particularly the P waves and the QRS complex

Both systolic and diastolic blood pressures are reduced by undernutrition but these changes, unlike the bradycardia are moderate and progressive In severe chronic undernutrition the systolic blood pressure is generally reduced 10 to 30 mm, with a smaller drop in diastolic pressure, the pulse pressure is invariably narrower[31] These changes have interesting relations to *problems of hypertension*[44]

The total circulatory function in starvation is, superficially at least well preserved Though there is a tendency to slight peripheral cyanosis, there are usually no complaints referred to the heart and no signs of impending or actual failure except in the terminal state Nevertheless detailed analysis indicates that the margin of safety is reduced and that the rate of circulation per unit of metabolic rate is substantially lowered[31]

In starvation it is common to observe fainting and giddiness particularly in the upright posture It is *surprising, therefore, to note that no inadequacy of circulatory* adjustment to posture is revealed by tilt table tests[45]

The restoration of cardiocirculatory function to normal by refeeding does not necessarily follow a simple path of reversal of the starvation changes When the rehabilitation diet is abundant there may appear signs of relative cardiac insufficiency at the time when the rate of gain of weight and of the basal metabolic rate are at their peaks The pulse rate in both rest and exercise and the venous pressure tend to exceed normal control *values and even frank* congestive failure may intervene[31] The sudden rise in the basal metabolic rate in rehabilitation may produce an intolerable strain on the heart. Full restoration of the heart is not as readily achieved as is the body weight.

44 Brozek J Chapman C B and Keys, A The Effect of Semi starvation on Cardiovascular Dynamics n Normotensi e and Hypertensive Persons J A M A to be publ shed.

45 Taylor H L Hensch l, A and Keys A. The Cardiovascular Response to Postu e and the Problem of Faintness and Syncope in the Semi Starved Individual, Am. J Physiol. 152: 141 149 1948.

may be achieved at surprisingly low figures The caloric deficit is apt to be grossly overestimated when calculated simply from caloric intakes

During nutritional rehabilitation the return of a sense of well being is coupled with an increase in voluntary physical activity, but the habit of energy conservation is not quickly broken An effort of will or coercion is often necessary to promote recovery in physical fitness by exercise The total daily metabolism tends to lag behind the proportional change in the basal metabolic rate in recovery

21 THE CARDIOVASCULAR SYSTEM

The response of the cardiac musculature to under nutrition has been mentioned in section 13 Changes in cardiac and circulatory function are obvious and in some respects more dramatic[31] It is well known that both total fasting and prolonged undernutrition tend to produce bradycardia and hypotension in rest The significance of these changes and other details of circulatory function have received little attention until recently

Starvation bradycardia is obvious in all instances except where there are extremely powerful heart accelerating forces at work, such as systemic infection great excitement or fear or impending circulatory collapse From the literature the impression is gained that the bradycardia is perhaps most profound in the earlier stages of severe undernutrition certainly the degree of bradycardia is not simply related to weight loss This was also indicated in the Minnesota experiment where the subjects average basal pulse rate of 34 9 per minute after 12 weeks rose to 37 8 after 24 weeks of semistarvation

The contrast with beriberi heart is important In beriberi there may be resting bradycardia but small physical exertion produces decided tachycardia In simple starvation exercise produces an increase in the heart rate but this is not disproportionate to the resting rate

The bradycardia of starvation does not involve heart block, the rhythm is of the sinus type[43] The rhythm is remarkable for its great regularity the variability of the length of the P R interval is smaller than normal

43 (a) Cardozo E L and Eggink P Circulation Failure in Hunger Edema Canad M A J 54 145 147 1946 (b) Simonson, E, Henschel A and Keys A The Electrocardiogram of Man in Semi Starvation and Subsequent Rehabilitation Am Heart J 35 584 602 1948

metical facility and so on revealed no changes in spite of the subjective impression of most of the men that their mental powers had been reduced

25 PERSONALITY AND EMOTION

Severe caloric inadequacy produces profound changes in the personality and the subjective state [46] Externally, the major characteristics are apathy depression and introversion Social contacts are avoided and sex interest declines sharply Psychiatric methods reveal besides the depression a well defined rise in the tendencies to hypochondriasis and hysteria Though the behavior is almost never aggressive it is easy to discern a tendency to a heightened irritability The behavior which would ordinarily be associated with increased irritability is suppressed by the overwhelming physical lethargy

It is difficult to appreciate the enormous preoccupation of the starving man with food and eating His thoughts tend to be exclusively dominated with these concerns Their expression may range from constant day dreaming about eating to extensions such as interest in scientific agriculture Niceties of behavior are brushed aside where they interfere with the full expression of these interests Even when the food supply is restored the concern about food persists for many months, a common expression is food hoarding even when there is not the slightest reasonable basis for this

Emotional crises and seriously disturbed behavior may arise from the conflict between the concentration on food and previously fixed convictions [46b] While these may result in irritated or antisocial behavior or even lead to self destructive impulses they do not partake of the character of the true psychoses

Personality changes in refeeding may be even more complex certainly the behavior may be more variable As the physical state improves the tendencies toward *depression and hypochondriasis diminish but they may* be returned in force by disappointment in the rate of recovery or threats of renewed food restrictions The return of physical vigor allows outward manifestation of formerly suppressed irritability At this stage these persons are far more difficult to manage and maintain

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46 ( ) Franklin J C Schiele B C. Brozek J and Keys A Observations on Human Behavior in Experimental Semi Starvation and Rehabilitation J Clin. Psychol 4 28-45 1948. (*b*) Schiele B C. and Brozek J Experimental Neurosis Resulting from Semi Starvation in Man Psychosom. Med. **10** 31 50 1948

22 STRENGTH AND COORDINATION

All psychomotor functions deteriorate in caloric deficiency, and the result is a serious impairment in working capacity Simple muscular strength, as measured in a single maximal exertion, declines steadily but not as dramatically as does the capacity for continued muscular exertions (endurance) In the Minnesota experiment the single effort strength of hands, arms and back declined about 30 per cent and the endurance in severe work which produces exhaustion in a few minutes fell as much as 85 per cent Collapse in the latter tests appeared to be due to muscular failure instead of the circulatory respiratory type seen in normal persons

Neuromuscular coordination is impaired by caloric undernutrition but the relative deterioration is less than in purely muscular capacity

The psychomotor functions are only slowly restored by refeeding When the body weight has been regained there may still persist a serious reduction in muscular endurance In young men full recovery in these respects takes the better part of a year

23 THE SPECIAL SENSES

Simple caloric starvation seems to have no deleterious effects on the special senses In the Minnesota experiment visual acuity was unaffected and there was no evidence of alteration in the senses of touch taste and smell Auditory acuity is ordinarily slightly improved at all frequencies, this was clearly demonstrated in the Minnesota subjects and is confirmed by less objective methods from famine areas The cause of the sharpened hearing may be mechanical associated with an enlargement of the free space in the auditory canal The improvement in hearing is lost during nutritional rehabilitation

24 INTELLECTIVE FUNCTIONS

Starving persons are ordinarily averse to any effort including that of the intellect, and their preoccupation with food and their own plight may give an impression of stupidity or mental incapacity Actually, however, there is no evidence for a decline in basic intellective capacity In the Minnesota experiment exhaustive studies on memory reasoning power verbal and arith-

have been few and of indifferent quality Opposing observations make it clear that no general conclusions are possible so far (e g, Edwards[50] versus Robertson and Tisdall[51]) Reports on the incidence and course of natural infections in underfed animals are similarly at variance[52]

Clinical records may be used to support or to oppose the claim that caloric deficiency, per se produces a decreased resistance to infection Some interesting recent data have to do with clinical experience in hospitals associated with prison camps in World War II where surgical procedures were often performed on persons in a deplorable nutritional state without unusual complications[53]

Morbidity and mortality records from World War II provide material for thought. In contradistinction to previous wars, pestilence was never rampant except where sanitation control was neglected No epidemics appeared in Western Holland or Greece at the times when there was mass starvation in those areas The diphtheria epidemic of 1946 appeared to affect the American occupation troops just as severely as the underfed populace Markowski[54] stated that typhus mortality was worse among the German guards than among the starving Russian prisoners at Hammerstein

On the whole the evidence to date suggests that there are various relations in different animals and with different organisms that the old association of famine and pestilence was largely due to sanitary faults and that in man caloric deficiency is not necessarily productive of a lowered resistance or a heightened susceptibility to infectious diseases in general

27 TUBERCULOSIS

As far into the past as there are records it is clear that *tuberculosis has always increased in periods of* severe food restriction The evidence for the period of the first World War is particularly valuable because it is possible in some cases to dissociate the factor of

50 Edwards J T Discussion on Nutrition and Its Effects on Infectious Disease *Proc Roy Soc Med* **30** 1046-1051 1937
51 Robertson E. C. and Tisdall F F Nutrition and Resistance to Disease Canad M A J **40** 282 84 1939
52 McCay C M Nutrition Ageing and Longevity Tr & Stud. Coll. Physicians Philadelphia **10**: 1 10 1942
53 Gottlieb, M L, Impressions of a POW Medical Officer in a Japanese Concentration Camp U S Nav M Bull **46** 663-675 1946
54 Markowski B Some Experiences of a Medical Prisoner of War *Brit. M J* **2** 361 363 1945

in an orderly social structure than when they were physically deteriorating These facts obviously have great sociologic importance.

26 UNDERNUTRITION AND RESISTANCE TO INFECTION

There is no aspect of undernutrition about which there is a more fixed common belief—and less objective evidence—than the question of the effect on resistance to infection The historical association of famine and pestilence has been so uncritically accepted as indicating cause and effect that there is a dearth of actual research and analysis The whole problem of nutrition and infection is enormously complicated,[47] obviously no broad generalizations are possible.

Properly, each infectious disease should be considered separately However only in the case of tuberculosis is there an appreciable amount of acceptable information Tuberculosis is discussed separately (section 27), here the other problems are noted briefly The evidence, such as it is, concerns (1) indirect suggestions from antibody titers precipitins, gamma globulin and the like, (2) animal experiments involving experimental infection (3) casual observations on natural infections in animals, (4) clinical reports and (5) morbidity and mortality data from famine areas

A long series of papers from Dr Paul Cannon's laboratory has stressed the importance of nutrition, particularly protein nutrition in antibody formation[48] Most of these animal experiments involved both severe caloric and protein deficiencies, the latter being more drastic than usually seen even in severe famine The exact relevance of these observations to human caloric deficiency is uncertain, the data themselves are contrary to some older studies[49]

Experimental studies with injections of micro organisms into animals in various states of nutrition

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47 Schneider H A. Nutrition and Infection, the Strategic Situation in Harris R W, and Thimann K V Vitamins and Hormones New York Academic Press Inc 1946 vol. 4 pp 35 70

48 Cannon P R. Wissler R. W Woolridge R L. and Benditt E P The Relationship of Protein Deficiency to Surgical Infection, Ann. Surg **120** 514 525 1944 Cannon P R. The Importance of Proteins in Resistance to Infection J A M A. **128** 360-362 (June 2) 1945 The Relationship of Protein Metabolism to Antibody Production and Resistance to Infection in Anson M L. and Edsall J T Advances in Protein Chemistry New York Academic Press Inc. 1946 pp 135 154

49 Zilva S S The Influence of Deficient Nutrition on the Production of Agglutinins Complement and Amboceptor Biochem. J **13** 172-194 1919

most that may be said is that the mortality statistics from starvation periods (e g, in Greece and the Netherlands) do not indicate any increase in cancer, the number of deaths ascribed to neoplasms is reduced in proportion to the total deaths [11]

29 HYPERTENSION AND CORONARY DISEASE

It has been noted (section 21) that caloric undernutrition normally produces a fall in the blood pressure What effect this may have on the incidence and course of hypertension and vascular diseases in general is an intriguing question There are many clinical impressions which are suggestive but these have little objective basis Mortality data from famine areas are of limited value because of the problems of certification, in most cases the figures are only grouped under such broad headings as 'cardiovascular disease"

The hospital records of Leningrad during the siege *of 1941-1942 and after are interesting In this period* of severe food shortage the hospital admissions for hypertension remained at about the ordinary level but the deaths from such conditions dropped sharply [44] *After the food supply was restored to much better levels* there was a veritable epidemic of hypertension and coronary deaths in Leningrad Transient hypertension during refeeding was also noted in the Far East [61] There is clearly an important area for research here

30 UNDERNUTRITION AND DIABETES

The association of diabetes with obesity and the *advantage of food restriction in this disease are well* established [62] These general relations are reflected in substantial changes in morbidity and mortality from diabetes during periods of food shortages even when these are not productive of real starvation [63] An improvement in the clinical condition of patients with established diabetes is quickly apparent when the food supply is restricted Beckert [64] compared 604 diabetic persons in Dresden in the summer of 1939 and again

61 Stapleton T Oedema in Recovered Prisoners of War Lancet 2: 850-851 1946

6 Josl n E P Dublin L I and Marks H H Studies in D abetes M ll tus IV Etiology Am J M Sc 192: 9- 3 1936 Newburgh L H Control of the Hyperglycemia of Obese D abetics by W ght R duct on Ann. Int Med 17: 935 942 1942

63 Stocks P D abet es Mortal ty in 1861 1942 and Some of the Factors Affect ng It J Hyg 43 242 47 1943

64 Beckert, W Ueber die H ufigk t des D abetes und die Auswir kungen der Lebensmitt lsrationierung auf dessen Verlauf Munchen med Wchnschr 87: 1333 1335 1940

food shortage from those of overcrowding, excessive labor, sanitation and medical care The data from Germany[55] are useful, but the analysis of Faber[56] for the situation in Denmark is most significant

Denmark's domestic food consumption in World War I decreased and then increased owing to the blockade The housing situation became extremely bad after the food supply was maintained at a good level Medical care was well maintained at all times Sharp changes in tuberculosis mortality were closely related to the level of food consumption and were relatively independent of overcrowding unemployment and the like

The data from World War II are adding much confirmation to the conclusion that tuberculosis morbidity and mortality are increased by caloric deficiency[57] In some cases changes in ascertainment distort the figures[41] but the general picture is convincing Clinical reports from areas of food shortages emphasize the frequency of a fulminating type of the disease Tuberculosis is certainly a most serious problem under any circumstance when there is a prolonged severe food shortage

28 UNDERNUTRITION AND NEOPLASTIC DISEASES

It is now well known that the incidence, growth and recurrence of several types of tumors in animals can be reduced or even prevented by exceedingly severe undernutrition[58] The prophylactic and therapeutic possibilities of caloric restriction in man have been argued[59] but there are serious difficulties in application In animal experiments inhibition of tumors has required the use of dietary levels so low as to retard growth greatly and to prevent estrus[60] While such levels are reached in human famine there are no data to show any important effect on the incidence or course of cancer in man The

55 Kirchner M Die Zunahme der Tuberculose Wahrend des Weltkrieges und ihre Grunde Zentralbl f d ges Tuberk—Forsch **131** 228 271 1921

56 Faber K Tuberculosis and Nutrition Acta tuber Scandinav **12**: 287 335 1938

57 Bourgeois P Vie J and Bellin A Les tuberculoses de famine etudiées dans les hopitaux psychiatriques de la Seine Bull et mém Soc med d hôp de Paris **59** 302 1943 Forel O La souse alimentation en France Rev Med De La Suisse Rom **63**: 47 1943 Dols and van Arcken[6] Brozek Wells and Keys[18] Markowski.[54] Kirchner[55]

58 Rusch H P and Baumann C A Nutritional Aspects of the Cancer Problem Nutrition Rev **4**: 353 355 1946

59 Potter V P The Role of Nutrition in Cancer Prevention Science **101**: 105 109 1945

60 Morris H P Ample Exercise and a Minimum Food as Measures for Cancer Prevention? Science **101**: 457 459 1945

the day Ascites is seldom seen except where there is severe anemia, intercurrent infection heart failure or decided hypoproteinemia The latter appears when the diet is unusually devoid of protein The edema itself is not particularly troublesome but it is a useful rough guide in evaluating the nutritional state in surveys, it is not a reliable or sensitive indicator in the individual During refeeding it tends to appear and disappear, being affected by exercise and posture as well as the dietary level

32 PROBLEMS OF REHABILITATION

The problems of nutritional rehabilitation following semistarvation periodically arise in acute form The practical necessities of relief allow scant opportunity for research and the factual information is extremely little In large scale relief operations the limitations of food materials emphasize the distinction between optimal and feasible programs the criteria must be those of efficiency and economy

The character of the diet in the preceding period of semistarvation is important In general there are vitamin deficiencies to be corrected in Asia whereas in Europe these tend to be much less prominent The severity of the state of undernutrition is a determining factor Almost any food items may be used for the majority of an underfed population but those persons in an extremely depleted state need easily digested food in frequent feedings Intravenous feeding is seldom desirable or necessary

Experience in Europe supports the observations in the Minnesota experiment where it appeared that calories in relative abundance are the first need The Minnesota subjects manifested a rate of recovery closely proportional to the calories supplied, at intakes of less than 2 700 calories daily recovery was exceedingly slow and apparently would have required more than a year In the Minnesota experiment it was found that intakes over 5 000 calories daily are unnecessary and may be dangerous In these young men engaged in light activity the optimal level appeared to be something like 3 500 calories

With adequate calories supplied in ordinary foods including breads made with low extraction flour the protein intake will normally be 70 gm or more per day At these levels the isocaloric substitution of protein

in the summer of 1940 A loss in weight was recorded in 62 2 per cent Clinically, 45 per cent were improved and only 5 per cent were worse In Belgium, moderate food shortages in the first three years of World War II were associated with a notable diminution in diabetes morbidity and a more favorable clinical course of this disease [65]

31 FAMINE EDEMA

Famine (hunger or war) edema was in a sense "discovered" in World War I, though it had been casually observed throughout the ages The simulation of this condition by protein depletion and a variety of evidences supporting Starling's theory of the role of colloid osmotic pressure in fluid balance led to almost universal belief, in spite of unheeded objections,[66] that famine edema is simply a result of hypoproteinemia. World War II however, contributed an unexpected denouement [67]

In starved persons edema may appear with relatively normal values for plasma protein concentration and the albumin fraction is not necessarily decreased Furthermore though on the average there may be some relation between the plasma protein level and the extent of the edema the relation is extremely rough and does not hold for individuals [68] Cardiac failure is not involved and the venous blood pressure is actually lower than normal Finally it should be noted that the edema fluid is extraordinarily low in protein

In ordinary cases of edema due to famine the edema is not so much an accumulation of tissue fluid as simply a retention of the prestarvation level of extracellular fluid, the edema tends to be the expression of a relative and not an absolute excess of fluid in the body It is probable that mechanical factors—elasticity and structure—outside the capillaries are responsible

The edema is ordinarily only moderate and is of the soft, dependent type being notable in the face in the morning and shifting to the lower extremities during

65 Brull L and Decharneux G Etude statistique sur mille cas de diabete Rev belge sc méd **15** 85 97 1943

66 Youmans J B Bell A Donley D and Frank H Endemic Nutritional Edema I Clinical Findings and Dietary Studies Arch Int. Med **50** 843 854 (Dec) 1932

67 Keys, A Taylor H L, Mickelsen O and Henschel A Famine Edema and the Mechanism of its Formation Science **103** 669 670 1947

68 Denz F A Hunger Oedema Quart J Med. **16** 1 19 1947 Keys, Taylor Mickelsen and Henschel [67]

CHAPTER XX

FLUID THERAPY

Relation to Tissue Composition and the Expenditure of Water and Electrolyte

DANIEL C. DARROW
and
EDWARD L. PRATT

Probably the proper use of water and electrolyte solutions is responsible for saving more lives of seriously ill patients than is the use of any other group of substances The beneficial effect may be direct or the patients may be supported until the pathologic process can be corrected by specific measures or surgical intervention Without a considerable knowledge of the physiology of body water and electrolytes physicians cannot properly treat diseases accompanied by dehydration edema acidosis alkalosis and shock or plan a rational therapy when fluids must be given parenterally or when electrolytes have been lost in sweat urine and gastrointestinal secretions

Previous concepts of the physiology of body fluids were dominated by two postulates which are now known to be erroneous First cellular membranes were regarded as practically impervious to sodium and potassium and second only alterations in extracellular fluids were thought to be readily accessible to fluid therapy During the past fifteen years analyses of tissue of experimental animals and determinations of balances of water and electrolytes in patients have *demonstrated that intracellular fluids* undergo fairly rapid changes in composition which alter profoundly the acid base equilibrium of extracellular fluids Furthermore the changes in composition of intracellular fluid particularly the loss of potassium and the changes in electrolyte concentrations affect the function of cells This new knowledge has provided a physiologic background which enables the physician to consider the composition of both extracellular and intracellular fluids in planning fluid therapy

for carbohydrate produced no discernible benefit in the Minnesota experiment. The extra protein supplement was limited to only 20 Gm a day, but there is no reason to believe that larger amounts would have important effects

Special vitamin supplements had no effect on the course of rehabilitation in the Minnesota experiment nor is there any objective evidence of value in the trials in Europe It is unnecessary to supply vitamin con centrates unless there is clinical evidence of vitamin deficiency and the relief diet itself is a poor source of vitamins

With the best of diets and rehabilitation treatment, full recovery from severe undernutrition is slow Body weight is regained long before functional normality is restored When the undernutrition lasts for many months and the weight loss is between 20 and 30 per cent, it is probable that complete rehabilitation, including restoration of working capacity, is seldom achieved in less than a year in young adults With older persons a slower recovery must be expected It is possible that children recover more promptly

33 LESSONS FROM CONTEMPORARY FAMINE EXPERIENCE

Acute and persistent problems of starvation and food shortages began to be apparent early in World War II The problems were not new but their over whelming nature has focused attention on them so that it should no longer be possible for them to be neglected by nutritionists in favor of the spectacular advances concerning individual nutrients But this reawakened interest is coming late so late that years of oppor tunity for definite research have been lost The data gathered in and immediately after World War II are valuable but they barely touch many points and on others leave confusion and uncertainty

Many of the accomplishments and the problems recognized but unanswered are indicated in several recent discussions and monographs [69] These may be examined with profit not only for the facts presented but for the indications of facts not collected the theories not critically examined and the questions not answered

69 Drummond J Fam ne Cond t ns and Malnutr t on in Western Europe J Roy Soc. Arts 94 470 477 1946 Boe ema J Med sche Ervar n en in N de l nd Tijdens de Be ett ng 1940 1945 Groningen J B Wolters 1947 Bigwood E J Enseignements de la guerre 1939 1945 dans le domaine de la nutrit on Liege Ed Desoer 1947. Tle ch

liver capillaries to protein Local changes in extracellular fluids are brought about by alterations in the capillary bed Lymph channels provide an alternate route for the return of vascular fluid which is entering the interstitial spaces and are concerned particularly in the removal of protein

Normally, the volume of the fluid of the vascular compartment is adjusted to the function of maintaining the exchange of metabolites in vital organs, first by redistributing the circulation according to the need but ultimately by altering the volume of plasma and extracellular fluids [2]

The kidneys play the chief role in the control of the volume and concentrations of body fluids However the renal regulation is merely the crucial activity in a complex process integrated by the regulation of the cardiovascular system, the neurohypophysis, the humoral and neural control of the blood pressure and capillary bed and the adrenal and other endocrine glands The control of the excretion of sodium and chloride determines the volume of extracellular fluids According to present evidence, about 85 per cent of the glomerular filtrate is reabsorbed without changing the osmotic pressure of the tubular urine of the proximal tubules Thus a large part of the reabsorption of water and sodium chloride is accomplished by processes that are intimately associated The rate of this reabsorption can apparently be augmented in proportion to the load which means according to the rate of glomerular filtration and plasma concentration In the distal tubules sodium, bicarbonate and water are absorbed by processes which are more or less independent of each other and are under independent regulation According to one theory [3] the distal tubules tend to reabsorb sodium in quantities which, though known to be variable tend to be relatively constant under some circumstances If this is true the excretion of sodium could be regulated in part by changes in the rate of glomerular filtration and the rate of reabsorption by the distal tubules If glomerular filtration supplies an amount of sodium to the distal tubules which exceeds the rate of reabsorption sodium will be excreted in the

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2 Landis E. M Brown E. Fauteux, M and Wise C Control of Venous Pressure in Relation to Cardiac Competence Blood Pressure and Exercise J Clin Investigation 25 237 1946

3 Wesson L. G Jr Anslow W P Jr and Smith H The Excretion of Strong Electrolytes Bull. New York Acad. Med. 24 586 1948

This paper will describe the chemical anatomy of both extracellular and intracellular fluids and will direct particular attention to the factors controlling the bal ance of sodium, potassium and chloride These ions seem especially important since they seem to determine the content of water and the acid base equilibrium of extracellular and intracellular compartments The clinical significance of changes in the composition of body fluids will be pointed out The final section will show how the new knowledge may be used to plan fluid therapy

I CONTROL OF VASCULAR AND EXTRACELLULAR COMPARTMENTS

The red cells and the plasma of the vascular com partment are about one fourth of the total extracellular constituents The blood plasma may be considered the prototype of all extracellular fluids and, although the red cells must be considered intracellular, their function is intimately connected with that of the plasma The movement of substances within the body and the exchange of water solids and gases with the outside environment is accomplished by the rapidly moving constituents of the vascular compartment Changes in body fluids are reflected in alterations in the volume and concentrations in the vascular compartment which provoke adjustments in the intake and the output by the kidneys as well as in the circulation and distribu tion of blood

The movement of substances between the vascular and interstitial fluids is governed by a balanced exchange between the capillaries and interstitial spaces[1] The movement of water and diffusible ions and mole cules out of the capillaries is favored by the hydrostatic pressure within the capillaries and the colloid osmotic pressure of the perivascular fluids the movement of these substances into the vascular compartment is favored by the colloid osmotic pressure of the plasma and the hydrostatic pressure of the perivascular fluids, which is exerted by the tissue tension An example of this balanced mechanism is seen in the portal circula tion, in which the low capillary pressure is balanced by a high colloid osmotic pressure of the perivascular fluid brought about by increased permeability of the

1 Starling E. H Fluid of the Body in Herter Lecture Chicago W T Keener & Co 1909

reabsorption of sodium in the absence of change in the rate of glomerular filtration[6] Although cardiac failure is regularly accompanied by retention of sodium, decrease in the rate of glomerular filtration does not always occur In any case it is probable that diminution of the functionally effective volume of the vascular compartment provides the stimulus which provokes the renal response leading to retention of sodium and water such as follows the assumption of the erect posture, exercise hemorrhage shock hypoproteinemic states and cardiac failure[7] The mechanism by which this response is achieved is the subject of heated debate and arduous research The following factors individually or in any combination may be involved reduction in renal blood flow, reduction in the rate of glomerular filtration increase in venous pressure, increase in the action of the hormone of the adrenal cortex on the kidneys and circulation and changes in blood pressure

The regulation of body potassium through renal function is just beginning to receive the attention that it deserves The kidneys can excrete more potassium than can be accounted for by the glomerular filtrate and though some potassium is always present in the urine the concentration may be less than that of the plasma. It is not clear whether the salt retaining hormone of the adrenal cortex increases the excretion of potassium by a direct effect on the renal tubules or whether potassium excretion is augmented indirectly when sodium excretion is decreased High serum potassium concentrations increase urinary potassium a rise in serum bicarbonate increases the urinary potassium Many types of diuresis lead to losses of this ion

The kidneys have the ability to control the acid base equilibrium of the blood by regulating the acidity of the urine This function demands adequate circulation and sufficient water and electrolyte According to one theory,[8] an acid urine is produced by exchange of hydrogen ions for other cations The same observa-

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6 Bradley S E. and Blake W D Pathogenesis of Renal Dysfunction During Congestive Heart Failure, *Am. J Med* **6** 470 1949

7 ( ) Landis[2] (*b*) Wesson[3] (*c*) Borst J G G The Maintenance of an Adequate Cardiac Output by the Regulation of the Urinary Excretion of Water and Sodium Chloride An Essential Factor in the Genesis of Edema, Acta. Med. Scand. **130** (Supplement 207) 1948. (*d*) Van Slyk D D *The Effects of Shock on the Kidney* Ann. Int. Med. **28** 701 1948.

8 Pitts, R. F and Lotspeich, W G Bicarbonate and Renal Regulation of Acid Base Balance, Am. J Physiol. **147** 138, 1946

urine On the other hand, if the rate of glomerular filtration is decreased and the distal tubular reabsorption remains the same, practically all the sodium which is filtered will be returned to the body At a given extracellular volume, increase in the concentration of sodium in plasma augments the rate of glomerular filtration and tends to increase urinary excretion of sodium The rate of water reabsorption in the distal tubules is under the control of the antidiuretic hormone of the hypophysis [4] Increase in electrolyte concentration in extracellular fluids and diminution of body water leads to decrease in urinary volume through the activity of the antidiuretic hormone Thus the theory is attractive because it provides a mechanism which can explain the regulation of both the volume and concentration of extracellular fluids The weakness of

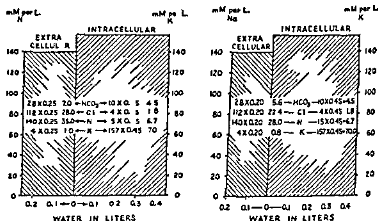


Fig 1 —Diagrammatic repre entation of body water and electrolyte in one k logram of t ssue of a normal baby (*left*) and of a *normal* adult (right)

the theory lies in the fact that the variations in the apparent rate of distal reabsorption of sodium are so great that experimental measurement of a constant rate cannot be substantiated because of inaccuracies in the methods and alterations produced by the observations themselves It is known that the salt retaining hormone of the adrenal cortex increases the rate of reabsorption of sodium presumably in the distal tubules [5] High venous pressure increases the rate of

4 Verney E B Croon an Lecture The Ant diuretic Hormone and the Factors Wh ch D termine Its Rele se Proc. Roy Soc London s B **135** 25 1947

5 (*a*) Kendall E. C Influence of Adrenal Co tex on Metabol sm of Water and Electrol;t s Vitam ns & Hormones **6** 277 1948 (*b*) Leaf A Couter W T and Newburgh L H Ev dence f Renal Sodium Excre t on by the N rmal Human Subj cts is Regulated by Adrenal Cort cal Activity J Clin Investig t on **28** 1067 1949

Figure 1 illustrates the relationships of extracellular and intracellular fluids of 1 Kg of tissue in babies and adults The extracellular concentration of sodium is represented on the ordinate for extracellular fluids while the intracellular concentration of potassium is represented by the ordinate for intracellular fluids The abscissas indicate the volumes of water in each instance The amounts of sodium and potassium in the two phases are indicated by the respective areas The amounts of the various electrolytes contained in each compartment are indicated by the concentrations multiplied by the volumes

Total water is slightly greater per kilogram in infants than in adults For the first months of life extracellular water of infants is about 30 per cent of the body weight Although the intracellular water of adults is probably slightly less than 45 per cent of the body weight this figure is suitable for all ages Actually, the total body water varies appreciably in normal persons The chief differences are accounted for by the fat content Since fat is deposited with relatively little water fat persons contain relatively less water per unit of weight However the quantitative relationships between the two types of fluid are essentially the same in normal persons except for the variations with age

Since the changes in body water and acid base equilibrium are explained chiefly by variations in water sodium potassium and chloride the discussions will be limited chiefly to these constituents First total intracellular sodium is about 7 millimols (mM) per kilogram approximately equivalent to the extracellular bicarbonate and equal to one fifth to one fourth of total extracellular sodium Normally intracellular sodium is variable since sodium can be transferred from intra cellular to extracellular fluids and vice versa The charts show the usual high normal value for intracel lular sodium Since the transfer is apparently accom plished without change in extracellular chloride the effect on extracellular fluid is to alter the amount of sodium available to form bicarbonate If total body electrolyte does not change transfer of extracellular sodium to intracellular fluids decreases the concentration of bicarbonate in extracellular fluids and transfer of intracellular sodium to extracellular fluids increases

tions can be equally well explained by the effect of removal of carbonate and bicarbonate on the p_H of the remaining constituents of the glomerular filtrate[9] The kidneys form ammonium, which may be substituted for other cations, and thereby save sodium and potassium, which would otherwise be necessary for the excretion of large amounts of anions This mechanism takes twelve or more hours to come into full activity The failure to reabsorb bicarbonate from the glomerular filtrate explains the excretion of an alkaline urine It is note worthy that formation of an alkaline urine fails to occur when there is a considerable deficit of electrolyte The excretion of bicarbonate leads to loss of potassium in the urine at least until there are considerable deficits of potassium in the body It is also clear that deficits of potassium lead to losses of chloride until the deficits of both potassium and chloride are considerable All the final regulations of the kidneys are inadequate when circulation is impaired or renal disease develops

II RELATION OF EXTRACELLULAR TO INTRACELLULAR WATER AND ELECTROLYTE

In order to enable the physician to visualize the quantitative relationships between extracellular and intracellular electrolyte a schematic representation of the composition of the body has been presented[10] The extracellular fluids are considered to have the composi tion of an ultrafiltrate of plasma The intracellular concentrations are represented per kilogram of the intracellular water of rat and cat muscle Data are available which indicate that the intracellular compo sition of muscle is approximately the same in young and mature cats and that human muscle has about the same composition as that of other mammals Some of the changes in intracellular composition accompanying variations in extracellular composition are known not to be the same in other tissues although similar changes are probably taking place Since the intracellular fluid of muscle is about 70 per cent of the total intracellular fluid and has about the same composition as other intracellular fluids the errors are not significant in depicting the relationship between extracellular and intracellular fluids for the body as a whole

9 Menaker W Buffer Equil bria and Reabsorpt on in the Production of Urinary Acidity, Am J Physiol. 154 174 1948

10 Darrow D C Body Flu d Phy ology The Relat on of Tissue Composit on to Problems of Water and Electrolyte Balance New England J Med. 233:91 1945

in muscle sodium and potassium depend on the accompanying changes in body water, sodium, potassium and chloride

Fourth there is a predictable relationship between the acid base equilibrium and the composition of muscle under certain circumstances [17] Figure 2 shows this relationship between the concentration of bicarbonate in serum and the intracellular sodium and potassium

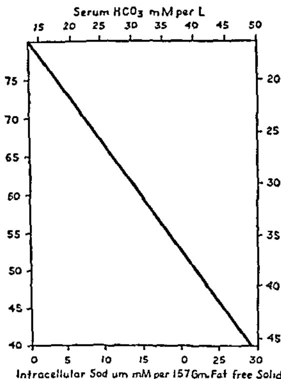


Fig 2 —The relat onsh p of the concentration of b carbonate n serum to the amount of sodium and potass um n the intracellular flu d of 1 Kg of ti ue The left ordinate scale represents cell potass um in millimols per 157 Gm. fat f ee solids The right ord nate scale represents serum b carbonate in m ll mols per l ter The d agonal l ne *represents the* rel t on of intracellular sod um to potassium. The bicarbonate values on the rd nate a e the best fit for the potas um wh le the b ca bonate values *on the absc sa are the best fit for the intracellular sod um.*

of 157 Gm of fat free solids Since this amount of fat free solids is associated with 450 Gm of intra cellular water the chart shows the intracellular composition for the same amount of intracellular water as figure 1 shows for 1 Kg of tissue The relationship

17 Dar ow D C. Schwartz, R Ianucci J F, and Coville F The Relat on of Se um B carbonate to Muscle Composition J Clin. Investigation 27: 198 1948

the concentration of bicarbonate in extracellular fluids Hence, shift of sodium from extracellular to intra cellular fluids and vice versa is an important mechanism for diminishing the variations in extracellular bicarbonate In many clinical situations, this mechanism functions in addition to the usually described buffers of the blood

Second, intracellular potassium in normal animals may be about 10 per cent lower than the values on the charts when there is no great disturbance in acid base equilibrium or body water The charts show the high normal value since this is the one usually found *in rats and cats Changes in intracellular potassium* may occur without detectable changes in intracellular sodium, though there is usually a reciprocal relation ship between intracellular sodium and potassium

Third, under abnormal conditions as much as one half of the intracellular potassium may be replaced by about two thirds of the equivalent amount of sodium This change in intracellular electrolyte was first dis covered in rats subjected to diets low in potassium [11] or receiving repeated injections of desoxycorticosterone acetate [12] Conditions leading to losses of body potas sium produce similar changes Evidence of loss of intracellular potassium has been found as a result of maintenance of body fluids by continuous intravenous injection of solutions containing sodium chloride and glucose [13] as a result of diarrhea [14] and accompanying certain adrenocortical tumors causing Cushing s syn drome [15] Under certain circumstances, alkalosis causes an increase in intracellular sodium and a decrease in intracellular potassium [16] Acidosis is also accompanied by loss of intracellular potassium when there are deficiencies of water and other ions [14] The changes *in* acid base equilibrium which accompany the alterations

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11 *Heppel L A Elect olytes of the Muscle and Liver in Potass um* Depleted Rats Am J Physiol **127**: 385 1939
12 Miller H C and Darrow D C Relat on of Muscle Electrolyte to Alterations n the Serum Potassium and to Toxic Effects of Injected Potassium Am J *Phys ol* **130** *747* 1940
13 Stewart T D and Rou ke G M Effect of La g Intravenous Infusions on Body Fluid J Cl n Inv st gat on **21** 197 1942
14 Darrow D C The Retent on of Elect lyte During Recovery from Severe Dehydration Due to Diarrhea, J Ped at **28** 515 1946
15 (*a*) McQuarrie I Johnson R M and Z egler M K Plasma and Electrolyte Disturbance in a Patient w th Hyperadrenocort cal Syn drome Cont asted with that Found in Addison s Disease Endocrinology **1** 762 1937 (*b*) W lson D M Pow r M H and Kepl r, E J Alkalosis and Low Potassium in a Ca e of Cushing s Syndrome Metabolic Study J Clin Invest gation **19** 701 1940
16 Darrow D C Changes n Muscle Compos tion in Alkalosis J Cl n Investigation **26** 374 1946

water that is $(25 - 5) \times 0.25 = 5$ millimols of sodium per kilogram of body weight, if the serum bicarbonate is 5 millimols per liter To this would be added the intracellular sodium (7 millimols), making a total *deficit of 12 millimols per kilogram* in a baby Except as modified by changes in extracellular volume, the relative deficit of sodium in acidosis is unlikely to be greater than 12 millimols per kilogram

Of the three ions under discussion, only potassium seems to alter cellular functions owing to specific ion effects High concentration of potassium in serum leads to *prolonged conduction time sharp high T waves and*, finally, heart block The heart block develops at concentrations of 10 millimols or more of potassium per liter of serum, but other minor evidence of cardiac dis turbance may develop at concentrations as low as 7 millimols per liter Unless there is renal insufficiency or shock high serum potassium is unlikely *to develop Low serum potassium leads to low voltages* in the electrocardiogram particularly of the T waves and to paralysis of the skeletal muscle These changes are probably always associated with deficit of potassium in the body as a whole In rats subjected to pronounced potassium deficiency dilated intestines developed and no stools were passed *These rats may die as if they had paralytic ileus* The evidences of intestinal paralysis are relieved by potassium [20]

Clinically potassium deficit can only be proved by demonstration of a greater relative loss of potassium than nitrogen during the development of the condition or a greater relative retention of potassium than nitrogen during recovery If body water and circulation are relatively normal deficiency of potassium is likely to be accompanied by *low concentration of potassium in serum Under these conditions* certain patients show paralysis of the skeletal muscles and abnormal function of the cardiac muscles Paralysis of skeletal muscles which is accompanied by low concentration of potassium in serum and relieved by administration of potassium salts was first recognized in familial periodic paralysis [21] A similar disturbance has been *described*

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0 Winter H A Hoff H E and Dso L. Effect of Potassium upon the Gastro ntest nal Moul ty Federat on Proc 8: 169 1949

21 Talbot, J C. *Periodic Paralysis*, Med cine 20 85 1941

was demonstrated for rats subjected to any one of the following conditions (1) loss of chloride, or primary metabolic alkalosis, (2) loss of sodium, or primary metabolic acidosis and (3) primary deficit of potassium Since water and other ions were abundantly available the relationship was demonstrated under conditions which permitted the kidneys to adjust body water and electrolyte when there was a deficit of one of the ions sodium potassium or chloride The relationship may be regarded as a biologic equilibrium, or steady state for these conditions The equilibrium must be regarded as biologic since it is not attained for several days and chemical equilibrium requires but several hours The chart (fig 2) is useful in illustrating the sort of changes which will tend to develop in the body with a deficit of one of these ions when the kidneys are able to maintain a relatively constant composition of the body fluids The chart is based on data from rats in which the relationship is readily demonstrated Clinical studies indicate that the relationship is manifested in humans In dogs[18] it is difficult to induce alkalosis in response to potassium deficiency though the same changes in cell composition are readily attained

It will be seen that deficit of chloride and deficit of potassium tend to produce the same changes in both extracellular and intracellular fluids At biologic equilibrium a deficit of one of these ions tends to lead to deficit of the other Intracellular sodium may reach levels several times the normal value and several times the equivalent of the bicarbonate in extracellular fluids This relationship is important first because alkalosis will tend to persist if potassium cannot be replaced and second because deficit of potassium will tend to lead to alkalosis if potassium is not restored Acidosis not accompanied by loss of potassium chloride or water leads to loss of intracellular sodium as well as relative deficit of extracellular sodium[19] Thus, acidosis due solely to deficit of sodium would have an extracellular loss equal to the decrease in bicarbonate concentration multiplied by the volume of extracellular

18 Muntwyler E Griffen G E Samuelson C S and Griffith L. E. Relation of the Electrolyte Compositions of Serum and Skeletal Muscle Federation Proc 8 231 1949

19 Darrow D C da Silva M M and Stevenson S S Production of Acidosis in Premature Infants by Protein Milk J Pediat. 27:43 1945

cortex in response to stress" [9] The release of potassium from the cells results in elevation of the concentration of this ion in the serum and increased excretion in the urine As a result of alkalosis a similar change in cellular composition takes place accompanied by urinary loss of potassium [17] It is not known whether the deficiency of potassium in alkalosis is initiated by the release of potassium from the cells or by altered renal function or both

The disturbances in acid base equilibrium have previously been described chiefly in terms of the relative contents of sodium and chloride in extracellular fluids Since sodium shifts between extracellular and intracellular fluids changes in acid base equilibrium are now known to involve changes within the cells The balances of potassium as well as those of sodium and chloride are involved in disturbances of the acid-base equilibrium

The physicochemical factors controlling the acid base equilibrium of the blood have been adequately discussed in a recent article by Singer and Hastings [30] as well as in textbooks [31] The present discussion will therefore emphasize the relationship of the changes in the acid base equilibrium of the blood to alterations in the composition of extracellular fluids and the accompanying changes in the cells

Changes in the acid base equilibrium may be defined as deviations from normal in the reaction or p_H of the blood The p_H is determined by the ratio of the carbon dioxide to the bicarbonate of plasma The concentration of carbon dioxide depends on the partial carbon dioxide pressure of arterial blood which normally is equilibrated with the carbon dioxide of residual alveolar air Hence, the carbon dioxide tension is subject to the regulation of pulmonary ventilation by the respiratory center The concentration of bicarbonate in serum is dependent on the amount of base (cations) available to form bicarbonate at the particular carbon dioxide tension with the particular amounts of blood electrolyte The base available to form bicarbonate is regulated by the kidneys In as much as we are chiefly concerned with

29 Selye H The General Adaptation Syndrome and Diseases of Adaptation, J Clin Endocrinol 6 117 1946

30 Singer R B and Hastings, A B An Improved Method of the Estimation of the Disturbances of the Acid Base Equilibrium of Human Blood Medicine 27 223 1948

31 Peters, J P and Van Slyke D D Quantitative Clinical Chemistry Baltimore, Williams & Wilkins, 1931

during the recovery from diabetic coma,[2] cholera[1] and sprue[24] It probably occurs in infantile diarrhea and in certain cases of nephritis[25] The effects of potassium deficiency on the heart are probably of great clinical significance First, there is a functional dis turbance leading to electrocardiographic changes, car diac dilatation and failure Later, actual necrosis of the myocardium develops[6] Prevention and treatment of the disturbances in the heart will probably prove to be the chief advantages of the addition of potassium salts to the usual fluid therapy, but prevention of alkalosis and tetany may be important in some instances

As will be discussed later, potassium deficiency develops because of an output greater than the intake as a result of diets low in potassium[2] or after prolonged maintenance of body fluids by infusions of glucose and sodium chloride solutions[13] Potassium deficiency may arise during normal intakes as a result of abnormal excretion in the urine in patients having certain adrenocortical tumors causing Cushing s syn drome[15] or in patients and animals receiving repeated injections of desoxycorticosterone acetate[6] and in cer tain cases of nephritis[5] and diabetes[22] Increased losses of potassium in the stools occur in most cases of diarrhea[14] Abnormal losses of potassium occur when intestinal secretions are lost through fistulas or suction drainage through catheters[27]

The cells tend to lose potassium and gain sodium when the circulation is impaired in dehydration or shock or when there is tissue anoxia[28] Possibly this transfer of potassium from the cells to the extracellular fluids and the accompanying urinary excretion is in part, dependent on the increased activity of the adrenal

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22 Holler J W *Potassium Deficiency Occurring During Treatment* of Diabetic Acidosis J A M A **131** 1186 (Aug 10) 1946

23 Huang K W and Mao I C Pa Pin (Transient Paralysis) Complicating Asiatic Cholera Am J M Sc **214** 153 1947

24 Harrison H E Tompsett R R and Barr D P Serum Potassium in Two Cases of Sprue, Proc Soc Exper Biol & Med **54** 315 1943

25 Brown M R Currens J H and Marchand J E Muscular Paralysis and Electrocardiographic Abnormalities J A M A **124:**545 (Feb 26) 1944

26 Darrow D C and Miller H C The Production of Cardiac Lesions by Repeated Injections of Desoxycorticosterone Acetate J Clin. Investigation **21** 601 1942

27 Peters J P The Structure of the Blood in Relation to Surgical Problems Ann Surg **112** 490 1940

28 Fox C L and Baer H Redistribution of Potassium Sodium and Water in Burns and Trauma and Its Relation to Phenomena of Shock Am J Physiol **151** 155 1947

high but it is not as high as when there is a similar deficit of potassium and no acidosis The difference between the deficits of sodium and potassium and the deficit of chloride is a measure of the deficiency of cations causing acidosis Since the deficit of sodium plus potassium may be greater than total normal extra cellular bicarbonate plus normal intracellular sodium *most patients with acidosis cannot rationally be treated with sodium chloride and sodium bicarbonate alone If intracellular potassium remains low the amount of* sodium in excess of chloride required to restore extra-*cellular bicarbonate would be more than the normal* total excess of sodium over chloride, including intra-*cellular sodium The changes in tissue composition* indicate clearly that replacement of potassium as well *as sodium and chloride is necessary in most cases of* metabolic acidosis

Metabolic Alkalosis—Metabolic alkalosis is produced by primary increase in the sodium available to form bicarbonate in serum Although metabolic alkalosis may be produced by relative excess of sodium it usually results from relative deficit of chloride. The commonest cause is loss of gastric juice by vomiting or suction drainage If sufficient water is available to permit renal adjustment potassium will tend to be lost from the cells and sodium will partially replace the intracellular deficit of potassium If the plan of therapy offers no opportunity for the body to replace the deficit of potassium alkalosis may continue despite the administration of both sodium and chloride because the biologic adjustment to the deficit of potassium leads to the maintenance of alkalosis by the kidneys A similar reaction by the kidneys explains the development of alkalosis as a result of primary deficiency of potassium. In either case recovery from alkalosis requires the replacement of potassium as well as chloride

Respiratory Acidosis—Respiratory acidosis results from primary increase in the carbon dioxide tension Probably the most frequent cause is depression of pulmonary ventilation owing to narcosis injury to the respiratory center or paralysis of the muscle of respiration However both acute and chronic respiratory acidosis may be produced by diseases of the lungs which lead to thickening of the alveolar walls exudates

the content of water and electrolyte in body fluids we shall neglect the relatively small changes in the buffering effect of the plasma proteins red cells and phosphate and emphasize the content of the tissues in sodium, potassium and chloride These ions are the chief factors determining the 'base available to form bicarbonate ' The cations available to form bicarbonate are the algebraic sum of total plasma cations minus the plasma anions, excluding bicarbonate that is ($Na + K + Ca + Mg$)—($Cl + HPO_4$ + proteins + sulfate + lactate + keto acids —) For many purposes, the changes in base available to form bicarbonate in the body as a whole are adequately defined by balances of sodium plus potassium minus chloride

Metabolic Acidosis—Metabolic acidosis is produced by primary decrease in the concentration of cations available to form serum bicarbonate It may be produced by relative increase in fixed acids or relative decrease in the concentration of total cations An increase in the anions may arise as a result of ingestion of acidifying salts through the endogenous production of organic acids owing to exercise anoxia hemorrhage keto acids in starvation ketosis and diabetes or through the retention of phosphates and sulfates in renal insufficiency A relative deficit of base may result from loss of intestinal or biliary secretions and through abnormal renal excretion

The changes in intracellular electrolyte in metabolic acidosis are only beginning to be studied Deficit of sodium alone such as is illustrated in figure 2 is apparently relatively rare If cation deficit is limited to sodium the deficiency is measured by the decrease in concentration of bicarbonate in extracellular fluids plus the deficiency of sodium in intracellular fluids The latter deficit is probably never greater than 7 millimols per kilogram Acidifying salts lead to retention of chloride without a corresponding retention of sodium This type of acidosis is essentially like primary sodium deficit The changes are illustrated by the effect of protein milk in babies[19] and the probable intracellular composition is illustrated in figure 2

Metabolic acidosis is usually accompanied by deficits of water sodium potassium and chloride When there is acidosis and deficit of potassium intracellular sodium apparently remains normal or may even be somewhat

diminution of oxygen saturation In respiratory acidosis due to lung disease there is unlikely to be a sufficiently rapid recovery of lung function to produce a true metabolic alkalosis during recovery

It is not known whether compensated respiratory alkalosis and acidosis produce changes in cell sodium and potassium It is likely that such is the case and that compensated respiratory alkalosis leads to diminution of cell sodium and compensated respiratory acidosis leads to increase in cell sodium and decrease in cell potassium

Disturbances in body water and electrolyte involve changes in the volume and electrolyte concentration which are just as important as the changes in acid base equilibrium Dehydration usually involves a decrease in electrolyte as well as water If the loss of electrolyte is proportionately greater than the loss of water there is a decrease in the concentration of electrolyte in serum This type of change may be called hypotonic dehydration Darrow and Yannet [32] produced loss of extracellular electrolyte without change in body water The concentration of sodium and chloride decreased in the serum while the concentration of serum proteins and hemoglobin increased The animals looked sick refused food and were weak The volume of urine decreased the rate of glomerular filtration decreased and the nonprotein nitrogen rose The cardiac output was strikingly decreased [33] It could be shown that the volume of extracellular water decreased while the volume of intracellular water increased The clinical picture was essentially the same as it is in the usual dehydration seen in patients The experiments are important because they emphasize that the central feature of hypotonic dehydration is loss of extracellular electrolyte

For practical purposes hypotonic dehydration may be considered to result from loss of proportionately more electrolyte than water although rare cases may involve little or no deficit of water With low concentration of serum electrolyte the cells contain more water than normal Statistically, the increase in cell water in

32 Darrow D C and Yannet H The Changes in Distribution of Body Water Accompanying Increase and Decrease in Extracellular Electrolyte, J Clin Investigation 14 266 1935

33. Danowski T S Winkler A W and Elkinton J R. The Treatment of Shock Due to Salt Depletion Comparison of Hemodynamic Effects of Isotonic Saline of Hypertonic Saline and Isotonic Glucose Solutions J Clin. Investigation 25: 130 1946

bronchiectasis and emphysema Since oxygen diffuses less rapidly than carbon dioxide, the arterial blood becomes less saturated with oxygen than normal when carbon dioxide accumulates Presumably, there is no change in body electrolyte in uncompensated respiratory acidosis

Respiratory Alkalosis—Respiratory alkalosis results from primary decrease in the carbon dioxide tension It is produced by excessive pulmonary ventilation, such as occurs during exercise, fever or a disturbance in the respiratory center as a result of infections of the central nervous system, tumors and drugs (salicylates) Overventilation may occur in hysterical patients or as a result of anoxia in cardiac failure or at high altitudes Uncompensated respiratory alkalosis presumably results in no change in body electrolyte

The disturbances in acid base equilibrium have been discussed as if only the carbon dioxide tension or the cations available to form bicarbonate were altered Actually, the alteration of one of these variables leads to compensatory variation in the others In metabolic acidosis, the respiratory center responds so as to increase the pulmonary ventilation and reduce the carbon dioxide tension The reduction is not sufficient to lead to a normal p_H of the blood In metabolic alkalosis, the respiratory center may reduce pulmonary ventilation but the reaction is limited because anoxia tends to be produced

On the other hand, the kidneys may alter the cations available to form bicarbonate in both respiratory acidosis and alkalosis In respiratory alkalosis the serum bicarbonate may be reduced fairly rapidly but as long as the disturbance in respiration persists the blood p_H remains normal or slightly alkaline However after the kidneys have produced the reduction in available cations the respiratory center may recover and respond normally The patient will then have true metabolic acidosis Since recovery from the effects of drugs such as salicylates may be rather rapid, respiratory alkalosis is likely to go through a phase of metabolic acidosis during recovery

In respiratory acidosis, the kidneys may increase the cations available to form bicarbonate to high levels (45 millimols per liter of serum) The blood p_H remains more acid than normal, and arterial blood shows a

tration in patients with edema leads to circulatory failure similar to that seen in hypotonic dehydration Renal function and circulation may be improved by raising the electrolyte concentration by giving sodium chloride and sodium bicarbonate Although hypertonic edema occurs increase in the concentration of extracellular electrolyte in patients with edema usually leads to further expansion of extracellular fluids It is likely that some patients with edema show the changes in cellular composition illustrated in figure 2 when there is change in serum bicarbonate concentration due to relative deficit of one ion

With these general comments as a background the changes in tissue composition in certain diseases will be discussed briefly Infantile diarrhea produces deficits of water sodium, potassium and chloride Considerable variation in the absolute and relative losses of these constituents is shown The serums may be hypotonic or hypertonic Metabolic acidosis is usually present in severe cases The balances during recovery in 8 severe cases showed an average deficit per kilogram of body weight of 125 milliliters of water 9 2 millimols of chloride 9 5 millimols of sodium and 10 millimols of potassium [38] Since the deficiency of sodium for the body as a whole is equivalent to the deficiency of chloride the acidosis is largely explained by transfer of extracellular sodium to the cells This conclusion is evident from the fact that the low concentration of bicarbonate indicates relative deficiency of sodium in extracellular fluids The deficiency of potassium is equivalent to about one seventh of the total estimated intracellular potassium content or about one fourth the equivalent of the total extracellular sodium The abnormally high intracellular sodium is not as great as the deficit of potassium would predict in figure 2 The deficit of potassium is sufficient to explain the development of acidosis with no deficit of sodium in relation to chloride The acidosis in infantile diarrhea is therefore dependent on deficit of potassium occurring in patients with a deficiency of water sodium and chloride

Figure 3 illustrates the probable state of body fluids in the dehydration of infantile diarrhea The deficit of extracellular water and electrolyte is about one fourth

38 Darrow D C, Pratt, E. L, Flett, J., Jr Gamble A. H and Wiese H F Disturbances of Water and Electrolytes in Infantile Diarrhea Pediatrics 3 1 9 1949

experiments producing deficit of extracellular electrolyte is only about two thirds as much as would reduce the electrolyte concentration of the intracellular fluids of muscle as much as the reduction of extracellular concentration [34] In chronic states of this sort the relationship may be somewhat different In any case, the disturbances in circulation, renal function and muscular strength are dependent not only on the decrease in extracellular water and plasma but also on decrease in electrolyte concentration [35] Hypotonic dehydration produces the picture called medical shock and responds to replacement of electrolyte, but the response is somewhat better when blood or plasma as well as electrolyte are given [36]

Hypertonic dehydration results when the loss of water is proportionately greater than the loss of electrolyte This leads to increase in the concentration of electrolyte in serum [37] It can be shown that relatively pure increase in extracellular electrolyte leads to increase in extracellular water and dehydration of the cells [32] Patients with hypertonic dehydration may show symptoms of shock but circulatory failure is less prominent than in hypotonic dehydration Patients and experimental animals with hypertonic serums show evidence of cerebral damage, death is likely to be accompanied by high temperature and respiratory paralysis

Edema is due to increase in the volume of extracellular water While the changes in composition of the intracellular fluids are not known, it is usually assumed that cellular structure is well preserved However, there is no reason to doubt that the cells undergo the same sort of changes in composition when the concentrations and acid base equilibrium of the serum are altered as has been shown to be the case when there is no increase in extracellular volume Thus, hypotonic edema should produce increased hydration of the cells while hypertonic edema should lead to dehydration of the cells There is evidence that low electrolyte concen

34 Yannet H and Darrow D C The Effect of Depletion of Extracellular Electrolytes on the Composition of Muscle Heart and Liver J Biol Chem **134**: 721 1940

35 (a) Darrow [32] (b) McCance R A V Experimental Sodium Chloride Deficiency in Man Proc Roy Soc London s B **119** 245 1936

36 Winkler A W Danowski T S and Elkinton J R The Role of Colloid and Saline in Treatment of Shock J Clin Investigation **25** 220 1946

37 (a) Darrow [2] (b) Rapoport S Hyperosmolarity and Hyperelectrolytemia in Pathologic Conditions of Childhood Am J Dis Child. **74**: 682 Dec) 1947

and electrolyte Nevertheless, it has long been known that adults lose large amounts of water, sodium, potassium and chloride in dysentery and cholera [40] Paralysis of skeletal muscles has been recognized following treatment of cholera,[23] and these paralyses were relieved by injections of potassium chloride Similar observations have been made in sprue [24] There can be little doubt that diarrhea in adults leads to striking deficits of potassium as well as sodium and chloride and that these losses are similar to those in infantile diarrhea

About twenty years ago, Atchley and others [41] showed that diabetic acidosis is associated with losses of potassium as well as sodium and chloride Holler [22] and others [42] recognized paralysis during recovery which was accompanied by low concentration of potassium in serum and was relieved by potassium salts We found that the retentions during recovery in 1 case of severe diabetic acidosis in an 8 year old girl were 100 Gm of water 8 millimols of chloride 12 millimols of sodium and 6 millimols of potassium per kilogram of body weight The serum concentrations of phosphorus decrease somewhat more strikingly during recovery from diabetic acidosis than do those of infants recovering from diarrhea The changes in body electrolyte in diabetic acidosis apparently resemble those of infantile diarrhea and the mechanism of hypokaliemia is dependent chiefly on depletion of intracellular potassium while the patient is becoming acidotic

The acidosis of renal failure has not been studied adequately from the point of view of changes in both extracellular and intracellular composition Patients with nephritis may show low concentrations of bicarbonate chloride and sodium but the intracellular changes accompanying these alterations are not known [43] The usual explanation of the electrolyte changes is failure of the kidneys to form a concentrated urine which conserves sodium chloride and preserves the

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40 Schmidt, C Charakterist k der epidemischen Cholera gegenuber v wandten Transsudationsanomal een Leips g u Mitau G A Reyher 1850

41 Atchley J L Loeb, R F Richards D W Jr B nedict E M and Dr coll M E On Diabetic Ac dos s a Detailed Study of Electrolyte Balance Follow ng Withd awal and Establ hment of Insulin Therapy J Cli Inv st gation **12**: 297 1933

42 Ni h lson W N and B anning W S Diabetic Acidos s J A M A **134**: 1292 (Aug 16) 1947

43 ( ) let s J P Salt and Water Metabol sm n Nephr tis Medicine **11**: 435 1932 (*b*) Tho n G Renal Failure Simulating Add son s Disease New England J Med **231**: 76 1944

of the normal content If infants with diarrhea are treated with sodium chloride and water alone the deficit of potassium persists and sodium enters the cells because of the deficit of potassium [38] If sufficient water is available for renal adjustment, high intracellular sodium and low intracellular potassium will result This will lead to high concentration of bicarbonate and low concentration of potassium in serum Alkalosis probably also aggravates the tendency toward development of low serum calcium [39] All these disturbances will disappear when food, with its high content of potassium, can be absorbed Indeed the success of treatment with solutions containing sodium chloride and sodium bicarbonate is dependent on sufficiently rapid recovery to permit feeding

If sodium chloride is given with insufficient water to permit renal adjustment, acidosis may persist or be aggravated Case 3 of a previous study [38] illustrates this course of events The patient had severe diarrhea and was treated with the addition of small amounts of sodium chloride to a milk mixture which gave too little water for a patient with diarrhea On admission, the concentrations of bicarbonate and chloride were, respectivbely 7 and 123 millimols per liter During recovery practically no change in body sodium or chloride occurred but 13 millimols of potassium and 100 Gm of water per kilogram of body weight were retained Since the diarrhea would have led to deficits of sodium and chloride if salt had not been given, the addition of sodium chloride to the food had prevented deficits of these ions from developing before the admission to the hospital and before the study was started The acidosis had probably been aggravated by transfer of sodium to the cells since sufficient water was not available to permit renal adjustment The persistent deficit of potassium explains the transfer of sodium to the cells On entry the patient had deficit of water and potassium leading to acidosis and hypertonic dehydration The picture was the result of treatment of diarrhea with sodium chloride and insufficient water

Adults with diarrhea have not been studied with methods which demonstrate the actual deficits of water

39 (*a*) Yannet H The Effect of Alkalosis on the Relationship Between Serum Calcium and Protein in Vivo J Biol Chem **137**: 409 1941 (*b*) Rapoport S Dodd K Clark M and Syllm I Postacidotic State in Infantile Diarrhea Symptoms and Chemical Data Am J Dis Child **73** 391 (April) 1947

the muscles lose potassium and gain sodium As was pointed out earlier, transfer of extracellular sodium to the cells produces metabolic acidosis when there is failure of renal adjustment of body electrolyte The cellular loss of potassium raises the concentration of potassium in serum If renal function is adequate, the potassium will be excreted in the urine A similar exchange of potassium for sodium in the cells occurs *in anoxia and explains the rise in concentration of*

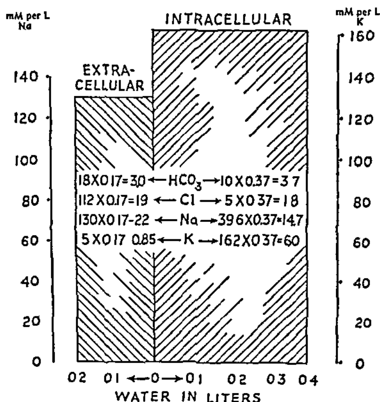


Fig 3—Diagrammatic representation of body water and electrolyte in 1 kg of tissue of a baby with dehydration resulting from diarrhea. The left ordinate scale represents sodium and the right ordinate scale potassium, both in millimols per liter

potassium in serum in peripheral vascular failure High concentrations of serum potassium are frequently found in diarrhea and diabetic coma before treatment is initiated despite the fact that the intracellular fluids are deficient in this ion This sort of reaction leading to urinary excretion of potassium explains in part the loss of this ion in diarrhea diabetic acidosis and other

acid base balance The inability to form an acid urine which contains ammonium is the chief explanation of the acidosis The inability to excrete phosphate aggravates this disturbance Certain patients with chronic nephritis have shown weakness and paralysis which is relieved by administration of potassium salts These patients have low concentrations of potassium *in the serum* [5] *and presumably in the muscles* [44] The logical explanation is that the kidneys are unable to conserve potassium This observation suggests that deficit of potassium may aggravate acidosis through the transfer of extracellular sodium to the cells in patients who have a deficit of sodium chloride and tend to lose potassium However, when there is oliguria the concentration of potassium in serum may rise to levels associated with heart block [45] Indeed potassium intoxication is one of the events leading to death in experimental anuria [45a b] and in some cases of uremia [45c]

All the symptoms of loss of extracellular water and electrolyte may be produced by immobilization of water and electrolytes at the site of an exudate or tissue injury Burns and crushing injuries to muscles are examples of disturbances of this type [46] It has been shown that the fluids which accumulate at the site of injury contain all the essential elements of extracellular fluids and plasma Although the fluids are not lost from the body as a whole the water and electrolytes are not available to the rest of the tissues Thus it is not surprising that traumatic shock with immobiliza tion of extracellular water and electrolyte and medical shock due to loss of extracellular electrolytes show the same clinical phenomena of peripheral circulatory collapse oliguria and anoxia of the tissues

When the circulation is interrupted or impaired by shock or exposure to cold [47] the intracellular fluids of

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44 Mudge G H and Vislocky K Electrolyte Changes in Human Striated Muscle J Clin Investigation **28** 482 1949

45 (*a*) Winkler A W Hoff H and Smith P K Toxicity of Orally Administered Potassium Salts in Renal Insufficiency J Clin Investigation **20** 119 1941 (*b*) Durlacher S H Darrow D C and Winternitz M C Effect of Depletion of Potassium on the Survival After Nephrectomy and Ureteral Ligation Am J Physiol **136** 57 194 (*c*) Keith N M and Osterberg A E The Tolerance for Potassium in Severe Renal Insufficiency A Study of Ten Cases J Clin Investigation **26** 773 1947 (*d*) Keith N M Clinical Intoxication with Potassium Its Occurrence in Severe Renal Insufficiency Am J M Sc **217** 1 1949

46 Blalock A Experimental Shock Arch Surg **22** 314 398 and 610 (Feb) 1931

47 (*a*) Fox [28] (*b*) Crismon J M and Fuhrman F A Distribution of Sodium and Water in Muscle Following Severe Cold Injury Science **104** 408 1946

the muscles lose potassium and gain sodium As was pointed out earlier, transfer of extracellular sodium to the cells produces metabolic acidosis when there is failure of renal adjustment of body electrolyte The cellular loss of potassium raises the concentration of potassium in serum If renal function is adequate, the potassium will be excreted in the urine A similar exchange of potassium for sodium in the cells occurs in anoxia and explains the rise in concentration of

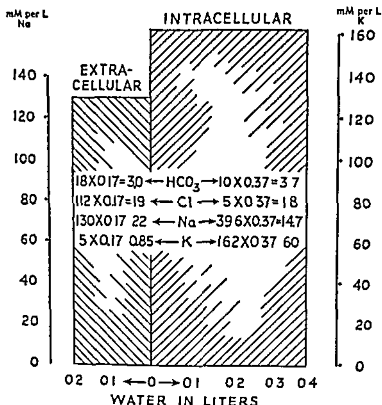


Fig 3—Diagrammatic representation of body water and electrolyte in 1 kg of tissue of a baby with dehydration resulting from diarrhea. The left ordinate scale represents sodium and the right ordinate scale potassium both in millimols per liter

potassium in serum in peripheral vascular failure High concentrations of serum potassium are frequently found in diarrhea and diabetic coma before treatment is initiated despite the fact that the intracellular fluids are deficient in this ion This sort of reaction leading to urinary excretion of potassium explains in part the loss of this ion in diarrhea diabetic acidosis and other

conditions However, the chief interest is the fact that internal shifts of sodium as well as loss of sodium from the body act together to produce acidosis

Alkalosis is usually the result of primary deficit of chloride produced by vomiting We have determined the retentions during recovery in 2 patients with congenital pyloric obstruction In both patients there was evidence of abnormally high intracellular sodium before treatment One patient retained a moderate amount of potassium during recovery, while the other did not Presumably some patients with alkalosis due to primary deficit of chloride will get enough potassium from food to prevent loss of potassium, but others will show deficiency of potassium as well as greater deficit of chloride than sodium[48] It should be remembered that *the presence of high intracellular sodium* in alkalosis indicates that the relative excess of sodium over chloride in the body as a whole is much greater than the excess in extracellular fluids as revealed by the serum concentrations of sodium and chloride The large amount of intracellular sodium explains the slow response of some patients to administration of sodium chloride The fact that the potassium deficit persists means that in accordance with the relationship depicted in figure 2 the kidneys will not excrete sodium so as to decrease the bicarbonate in the serum until potassium is available

Prolonged duodenal drainage after operative procedures provides the conditions for development of alkalosis with potassium deficiency The removal of the gastric fluid depletes the body of more chloride than sodium and produces alkalosis The *administration of* sodium chloride facilitates the excretion of potassium by the kidneys While sodium chloride is usually *administered in sufficient amounts to replace* extracellular electrolyte, the development of potassium deficiency alters the renal function so that metabolic alkalosis persists The alkalosis probably develops because of a chloride deficit but it persists because of a deficiency of potassium These patients have low concentrations of potassium in serum Clinical and

48 (*a*) Danowsk T S G eenman L Peters J H Gow R, and Mateer F Met bolic Stud es in Infants Recove ng from Vom ting J Cl n. Investigation **28** 777 1949 (*b*) Pearson O H and El el L P Postop rative Alkalos s and Potass um Defic ency J Cl n. Investgation **128** 803 1949 (*c*) Darrow [7]

chemical improvement follows replacement of potassium as well as sodium chloride [49]

McQuarrie and others [15a] called attention to certain patients with Cushing s syndrome who have alkalosis refractory to administration of sodium chloride but responding to potassium salts The serums show not only high concentrations of bicarbonate but low chloride and potassium Kepler and others [50] studied a patient who recovered from alkalosis after removal of an adrenocortical tumor but in whom alkalosis again developed when metastases became manifest Analyses of the muscle of these patients would probably show low potassium and high sodium The patients suffer from primary deficit of potassium produced by certain adrenocortical steroids which increase the excretion of potassium by the kidneys The same picture can be produced by repeated injections of desoxycorticosterone acetate [17] or less readily by diets low in potassium The experimental animals receiving desoxycorticosterone acetate show high intracellular sodium and low potassium in muscle together with definite alkalosis of the serum

Edema represents chiefly an expansion of the extracellular water and electrolyte The mechanisms promoting the formation of edema which act locally in the exchange of fluid between the capillaries and interstitial fluids are increased hydrostatic pressure in heart failure and venous obstruction decrease in the serum concentration of albumin in nutritional edema nephrosis nephritis and liver diseases, the presence of interstitial proteins in abnormal amounts in allergic reactions myxedema and acute nephritis and decreased absorption of fluids by the lymphatics in some diseases Ultimately the volume and concentration of body fluids is controlled by the kidneys

III EXPENDITURE OF WATER AND ELECTROLYTE

Since the maintenance of body water and electrolyte demands that the intake equal the output the factors

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49 Burnett, C. H Burrows B A. and Commons R S Studies of Alkalosis I Renal Function During and Following Alkalosis Resulting from Pyloric Obstruction Burnett C H Burrows, B A. Commons, R. S and Towery B T II Electrolyte Abnormalities in Alkalosis Resulting from Obstruction to be published.

50 (*a*) McQuarrie.[14a] (*b*) Kepler E. J Sprague, R. G Clagett, O T Power M H Mason, H L. and Rogers, H M. Adrenal Cortical Tumor Associated with Cushing s Syndrome J Clin. Endocrinol. 8:499 1948

controlling the expenditure of water and electrolyte must be understood by physicians The important path ways of losses of water and electrolyte are (1) the lungs and *skin*, (2) *the urine and* (3) the gastro intestinal tract The loss from the lungs and skin may be divided into the insensible losses occurring when there is no sweat and those involving activity of sweat glands The insensible water loss, excluding sweat is roughly correlated with heat production so that 42 Gm are lost for each 100 calories produced[51] Insensible water loss is accompanied with negligible losses of electrolyte

The substances presented to the kidneys for excre tion are chiefly the end products of protein metabolism together with other osmotically active substances, of which electrolytes are the most important Renal load *is proportional to the metabolic mixture being burned in the body* Although different diets may contain dif ferent amounts of protein and electrolytes the ordinary mixed diets of patients are sufficiently alike to permit an approximate estimation of the renal load from the calories During fasting the renal load consists largely of the end product of protein metabolism together with electrolytes freed by the breakdown of the tissues The metabolic mixture during fasting probably varies some what with age and nutritional status When all other food is omitted administration of glucose reduces the renal load not only to the extent that protein is spared but also by abolishing ketosis which requires excretion *of these acids together with electrolyte*[52] *Minimal* protein metabolism is attained by administration of 4 to 5 Gm of carbohydrate per 100 calories metabolized During fasting the renal load depends on caloric pro- duction except that the load is diminished by admin- istration of glucose The concentration of the urine determines the volume of water excreted by the kidneys and is dependent on the renal load, the water intake and the ability of the kidneys to form either a concentrated or *dilute urine The amount of urinary water which* contains a given load varies inversely with the urinary concentration[5 b]

51 Newburgh L H and Johnson N W The Insensible Loss of Water Physiol Rev 22 1 194

52 (a) Gamble J L *Physiological Information from Studies on the Life Raft Ration in Harvey Lectures 1946-1947* Lancaster Pa Science Press Printing Company 1947 p 247 (b) Gamble J L and Butler A Measurement of Renal Water Requirement Trans A Am Physicians 58 157 1944

Stool water is dependent chiefly on the residue of the diet which in general is proportional to the caloric intake During fasting stool water is negligible unless there is diarrhea Normal stool water is about 4 Gm per 100 calories of diet and is such a small part of the total water expenditure that it is negligible for most purposes

Figure 4 shows the urinary volume per 100 calories on the ordinate and the urinary concentrations on the abscissa The area labeled diet gives the urinary volumes with the usual adult diet The area marked glucose gives the urinary volumes during omission of all food except enough glucose to produce maximal reduction of renal load Complete fasting requires intermediate volumes Artificially fed infants fall in the lower part of the area marked diet Because of the low content of protein and electrolyte in human milk the renal load of the breast fed infant is almost as low as that indicated by the glucose area.

The total water requirement is calculated as in the following manner 1 The caloric production is estimated from the age weight activity and food intake 2 The area appropriate for the diet fasting or glucose feeding is chosen 3 From the chart the urinary volume per 100 calories is obtained for an appropriate urinary concentration—usually at a specific gravity of 1 012 4 This volume is multiplied by one hundredth of the estimated caloric production to obtain the urinary volume 5 For each 100 calories metabolized 42 ml of water are required to cover the insensible water loss The sum of the urinary volume and the insensible water loss gives the water expenditure excluding sweat stool water and abnormal losses Since complete absence of sweat is unlikely 15 to 20 ml per 100 calories metabolized should be added to cover total water expenditure in the absence of abnormal losses or large volumes of sweat.

For the normal person who is without sweat and on a normal diet and who has a urinary specific gravity of 1 012 the previous calculations indicate that water expenditure is 126 ml per 100 calories or 140 ml assigning a small allowance for sweat and stool water Since babies metabolize about 100 calories per kilogram this figure gives the water requirement of infants per kilogram of body weight An adult metabolizing 3 000 calories would require 3 800 to 4,200 ml or 54 to 60 ml.

per kilogram if the metabolism is 43 calories per kilogram If the values are calculated for a urinary specific gravity of 1 024, a baby would require 88 ml per kilogram of body weight if there is no sweating An adult would require 2 650 ml, or 38 ml per kilo gram of body weight These figures are minimal, except as modified by reduced caloric production or diets giving low renal loads In calculating the water intake it should be kept in mind that the water available for expenditure is equal to the water intake plus the water of oxidation The water of oxidation is about 12 ml per 100 calories metabolized of the usual meta bolic mixture During fasting a small amount of water is made available for expenditure by decrease in tissue water

The usually prescribed intake of infants is 150 ml per kilogram, which would lead to a urinary specific gravity of about 1 008 if there were no sweating or abnormal losses A similar intake per 100 calories metabolized in an adult would be 4 500 ml At this level of intake, the kidneys could, if so required, save about 62 ml of water per 100 calories metabolized, or a total of 1 860 ml for the average adult This level of intake may be necessary for most infants since they cannot readily make known their need for water Adults will voluntarily regulate their intake so as to lead to a moderately concentrated urine It may be advisable to prescribe as high an intake as this for children and adults if sweating or abnormal losses are likely to occur

Unless there is considerable sweating or abnormal loss the intake of electrolyte with the diet or that freed from breakdown of tissues during fasting is sufficient to replace the losses through skin stools and urine The urine can be rendered practically free of sodium and chloride Data on the ability of the kidneys to conserve potassium are meager but it appears that the normal kidney can produce urine which contains potassium at no greater concentration than that of the serum Therefore the minimal urinary losses of electrolytes are 0 2 millimol of chloride and sodium and 0 4 milli mol of potassium per 100 calories metabolized The minimal daily losses in 1 year old infants are about 2 millimol of sodium chloride and 4 millimol of potassium Corresponding adult losses would be about fourfold When food is taken stool losses are about

0 1 millimol of sodium chloride and 0 4 millimol of potassium per 100 calories Stool electrolyte is negligible during fasting unless there is diarrhea.

Metabolic studies indicate that the insensible water loss is slightly greater than can be accounted for by caloric production under ordinary circumstances in infants,[53] children[54] and adults[51] This observation indicates that a moderate amount of sweat is usually being formed An average estimate is 10 ml of water, 0 5 millimol of sodium and chloride and 0 2 millimol of potassium per 100 calories metabolized The

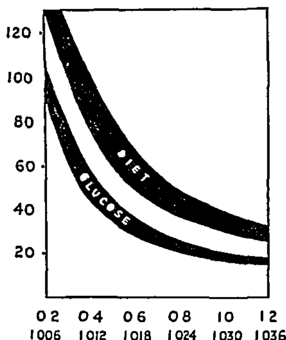


Fig 4—The urinary volume requ red to excrete the solids presented to the kidn ys for excret on by the m tabolism of 100 calories. The ordinate scale represents mill l ters of w t r per hund ed calories, the upper abscissa scale represents osmoles per liter and the lower spec fic gravity

average sweat losses in adults would be 300 milliliters of water, 15 millimol of sodium and chloride and 6 millimols of potassium

Allowances for growth are of little practical significance inasmuch as the usual diets provide abundant water and electrolyte The daily retentions during the

53 Cooke R E. Pratt, E. L. and D rrow D C. The Metabolic Response of Infants to Heat Stress Yale J B ol. & Med to be publ hed.
54 Macy I G Nutr tion and Chem cal Growth in Childhood, Charles C Thomas Publish r Springfield, Ill. 1946.

first year of life are 10 milliliters of water 0 6 millimol of sodium, 0 4 millimol of chloride and 1 5 millimols of potassium During periods of rapid growth, the retentions may be twice these values, and from the third to the tenth year they may be about half as great

In summary the water requirements can be predicted fairly confidently for normal conditions by the calculations described in the discussion of figure 4 The minimal losses of electrolyte in a 1 year old infant are probably about 8 millimols each of chloride, sodium and potassium, or about 0 5 Gm of sodium chloride and 0 33 Gm of potassium The average minimal losses of an adult would be 2 5 Gm of sodium chloride and 1 5 Gm of potassium Probably, somewhat larger amounts should be given since minimal expenditure cannot be anticipated

Under normal conditions without sweating about two thirds of the insensible water loss occurs by diffusion through the skin The rate of water loss from the respiratory tract depends on the volume of respiratory exchange and the content of water of the inhaled and exhaled air These are in turn dependent on the temperature and humidity of the environmental air since the exhaled air is about 88 per cent saturated with water at 33 C When there is hyperpnea, the magnitude of the water losses through the lungs is difficult to measure but probably reaches values five times as great as the normal rate [55] In estimating the importance of the losses from the lungs it should be remembered that an increase in the loss of water from the lungs may be partially compensated by a decrease in the activity of the sweat glands Water loss from the lungs is not accompanied by loss of electrolyte

The insensible loss of water from the skin is dependent chiefly on a gradient for diffusion through the skin This is dependent chiefly on skin temperature if the surface is dry A small amount of electrolyte is lost from the skin when there is no sweat presumably through desquamation though there may be minimal activity of sweat glands as well Losses of water in sweat are discussed in the excellent book by Adolph and associates [56] In the thermal balance of the body

55 Burch G E Rate of Water and Heat Loss from the Respiratory Tract of Normal Subjects in a Subtropical Climate Arch Int Med 76 308 (Nov) 1945

56 Adolph E F and others Physiology of Man in the Desert New York Interscience Publishers Inc 1947

the skin acts like a black body with a temperature of about 33 3 C (92 F) The body gains heat from the environment and objects above this temperature and loses heat to objects and environment below this temperature At an environmental temperature of about 26 7 C (80 F), body temperature is maintained without sweating and without more heat production than that characteristic of rest At a given temperature, the radiant energy of direct sunshine may add as much as 50 per cent to the heat balance when only indirect energy from the sky is acting on the body The volume of sweat is normally produced in amounts sufficient to maintain the body temperature when the metabolic production of the heat and the positive heat balance from the environment are greater than the losses produced by evaporation of the insensible water and by the heat losses through radiation conduction and convection The efficiency of the evaporation of sweat is not seriously impaired until humidity is greater than 80 per cent Air currents accelerate the rate of evaporation and the exchange of heat with the environment

The volume of sweat may reach 2 5 liters an hour in men at hard work at a high environmental temperature A few measurements on normal infants kept practically nude showed that raising the environmental temperature from 26 6 to 33 3 C (80 to 90 F) increased the loss of water from the lungs and skin from 48 to 108 ml per kilogram per day Presumably at least as much as 60 ml of sweat per kilogram per day was produced at the higher temperature Adults sitting in the shade at similar temperatures showed comparable sweating per unit of heat production [56] The calculated losses of sweat in infants with diarrhea studied in hot weather in August in Galveston Texas and Dallas Texas averaged 70 ml per kilogram per day [88]

When the environmental temperature is higher than 33 3 C (92 F) all the loss of heat is accounted for by evaporation of water and light clothing diminishes the amount of sweat by prevention of the loss of drops of sweat from the body surface and decrease of the addition of heat from the environment At lower temperatures clothing sometimes increases the volume of sweat by decreasing the loss of heat by radiation and convection Mere observation of the skin is made-

first year of life are 10 milliliters of water 0 6 millimol of sodium, 0 4 millimol of chloride and 1 5 millimols of potassium During periods of rapid growth the retentions may be twice these values, and from the third to the tenth year they may be about half as great.

In summary the water requirements can be predicted fairly confidently for normal conditions by the calculations described in the discussion of figure 4 The minimal losses of electrolyte in a 1 year old infant are probably about 8 millimols each of chloride sodium and potassium or about 0 5 Gm of sodium chloride and 0 33 Gm of potassium The average minimal losses of an adult would be 2 5 Gm of sodium chloride and 1 5 Gm of potassium Probably somewhat larger amounts should be given, since minimal expenditure cannot be anticipated

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55 Burch G E. Rate of Water and Heat Loss from the Respiratory Tract of Normal Subjects in a Subtropical Climate, Arch. Int. Med 76 308 (Nov) 1945

56 Adolph E. F and others Physiology of Man in the Desert, New York, Interscience Publishers, Inc. 1947

urine of fixed specific gravity, the water for urine formation is limited to the volumes which will contain the substances to be excreted at the fixed specific gravity (usually at a specific gravity of 1 010 to 1 012) As is shown in figure 4 (part I page 473), the solids produced in the metabolizing of 100 calories will require about 85 ml of water if the specific gravity of the urine is 1 012 A total water intake of about 150 ml. per 100 calories metabolized is required for urine of this specific gravity This amounts to about 4 liters in an active adult.

Electrolyte disturbances are likely to develop in patients with chronic nephritis because the kidneys not only are unable to conserve water but also waste sodium chloride[43] and in some cases potassium[3] Severe diminution of the rate of glomerular filtration is also accompanied by inability to excrete adequately sulfate, phosphates and other acids Administration of sodium chloride may overcome the losses of sodium chloride but probably aggravates the tendency to excrete potassium. Furthermore renal insufficiency often is accompanied by inability to form an acid urine and to excrete ammonium in order to save sodium and potassium.[43] *The retention of phosphate and other acids and the* wastage of sodium and perhaps potassium produces metabolic acidosis The diagnosis of potassium deficiency has been established in a few patients with nephritis in whom paralysis accompanied by low concentration of potassium in serum developed The paralysis and weakness were relieved by administration of potassium salts[25] On the other hand oliguria and anuria may lead to retention of potassium and a rise in the serum concentrations to levels producing heart block[59]

During convalescence from anuria and in some types of nephritis[60a b c] large volumes of urine may be formed which contain little sodium and chloride. In these patients the usual intake of salt may be sufficient to lead to high serum concentrations of these ions A

59 Winkler[46a] Keith[46c] Keith.[46d]

60 ( ) Luetscher J A., Jr and Blackman, S S., Jr Severe Injury to the Kidneys and Brain Following Sulfathiazole Administration High Serum Sodium and Chloride and Persistent Cerebral Damage, Ann. Int. Med. 18 741 1943 (b) Albright, F Consolazio, W V Coombs F S Sulkowitz H W and Talbot J Metabolic Stud and Therapy in a Case of Nephrocalcinosis with Rickets and Dwarfism Bull. Johns Hopkins Hosp. 66 7 1940 ( ) Butler A. M Wilson J L., and Farber S Dehydration and Acidosis with Calcification of Renal Tubules, J Pediat. 8 489 1936

quate to detect the onset of sweating or to estimate its amount For a lightly clothed person at a room temperature of 85 to 90 F an allowance for the loss of 50 ml of sweat for each 100 calories metabolized is apparently indicated Since operating rooms are likely to be quite warm, water loss in sweat may be con siderable during operative procedures Air condition ing and avoidance of overheating are, therefore important therapeutic measures, particularly for patients with disturbance in the metabolism of water and elec trolyte.

The quantity of electrolyte in sweat has been found to be so variable that any prediction of the composition of sweat is difficult and unreliable For clinical purposes, the concentration of sodium and chloride may be assumed to be 25 to 50 millimols per liter and that of potassium 15 millimols These values may be somewhat high for normal acclimated persons Actu ally analyses of sweat indicate that the concentration of sodium and chloride may vary from 5 to 100 milli mols per liter There is evidence that acclimatization to hot weather is accompanied by a tendency to excrete a less concentrated sweat [57] Recent work indicates that the concentrations of sodium potassium and chloride in sweat are influenced by the adrenocortical hormones Conn has shown that patients with adrenal insufficiency have high concentrations of sodium and chloride and low concentrations of potassium in the sweat induced by heat In contrast patients with adrenocortical tumors or patients receiving pituitary adrenocorticotrophic hormones or desoxycorticosterone acetate have concentrations of sodium and chloride that are lower than normal and concentrations of potassium that are higher than normal [58]

Abnormal urinary losses of water and electrolyte occur when there are abnormal loads or disturbances in renal function Abnormally large renal loads are produced by ketosis and glycosuria Diets high in protein or electrolyte increase the urine volume. Fifty grams of glucose or 9 Gm of sodium chloride require about 250 ml of water for excretion in urine which is max imally concentrated When renal disease produces a

57 Moreira, M Johnson R. E. Forbes A. P and Consolazio, F Adrenal Cortex and Work in Heat, Am. J Physiol. 143 169 1945

58. Conn, J W The Electrolyte Composition of Sweat, Clinical Implication as an Index of Adrenal Cortical Function Arch. Int. Med. 83 416 (April) 1949

cardiac failure noted in patients receiving desoxycorticosterone acetate Paralysis due to deficiency of potassium has been noted in animals receiving desoxycorticosterone acetate[66b]

During peripheral circulatory failure (shock) there are disturbances in renal function The rate of glomerular filtration decreases and the concentration of non-protein nitrogen rises[67] Alteration in renal circulation during shock seriously interferes with renal regulation of electrolyte concentrations[7b] Furthermore, accompanying local changes in the tissues potassium leaves the cells and is replaced by somewhat less than equivalent amounts of sodium This produces metabolic aci-

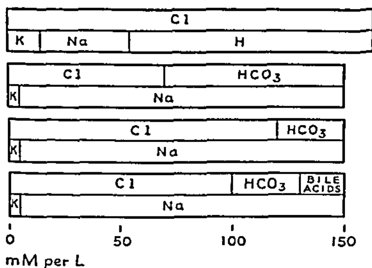


Fig 5—Diagrammatic representation of the concentrations of gastro-intestinal secretions From the top down gastric, pancreatic, small intestinal and hepatic bile.

dosis and leads to high concentration of potassium in the serum[28] As long as urine is excreted a high serum potassium leads to urinary excretion of this ion Loss of potassium in the urine in diarrhea and diabetic acidosis is in part explained by this type of reaction[38] Further study will probably show that disturbances in renal function explain other changes in body water and electrolyte that develop in shock

Abnormal losses of water and electrolyte from the gastrointestinal tract occur as a result of vomiting,

67 (a) Harrison[64] (b) Richards D W The Circulation in Traumatic Shock in Man in Harvey Lectures 1943 1944 Lancaster Pa Science Press Printing Company 1944 p 217

similar reaction occurs in certain infants as a result of a congenital anomaly in tubular function causing obligatory polyuria [61a, b, c] The polyuria of diabetes insipidus on the other hand is not often accompanied by electrolyte disturbances because the tubules function normally in preserving electrolyte concentrations of the serum The tubules reabsorb sodium chloride when the intake of water is high and the intake of salt is low and fail to reabsorb sodium chloride if the intake of salt is high Patients with diabetes insipidus merely have difficulty in drinking enough water to replace the excessive losses in the urine [6]

Adrenal insufficiency leads to deficits of sodium and chloride because of the inability of the kidneys to conserve these ions [63] Accompanying this loss, there is a tendency toward retention of potassium especially when circulatory failure develops [64] Renal function may be restored though inadequately, by administration of sodium chloride [63] Desoxycorticosterone acetate not only enables the kidneys to reabsorb sodium and chloride from the glomerular filtrate but also increases the rate of excretion of potassium [65] This may lead to deficit of potassium particularly if large amounts of sodium chloride are given [66] The deficits of potassium may lead to low concentration of chloride and potassium in the serum and to high concentration of serum bicarbonate and serum sodium when renal adjustment to deficit of potassium is attained in the presence of abundant sodium chloride (fig 2) Certain adrenocortical tumors have a similar effect [15] The deficiency of potassium especially when large amounts of sodium chloride are given probably explains some of the instances of

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61 (*a*) *Waring A J Kajdi L and Tappan V A Congenital* Defect of Water Metabolism Am J Dis Child **69** 323 (May) 1945 (*b*) Dancis J Birmingham J R and Leslie S H Congenital Diabetes Insipidus Resistant to Treatment with Pitressin Am J Dis Child **75** 316 (March) 1948 (*c*) Williams R H Nephrogenic Diabetes Insipidus Occurring in Males and Transmitted by Females J Clin Investigation **25** 937 1946

62 Deleted on proof

63 Loeb R F The Adrenal Cortex and Electrolyte Behavior Bull. New York Acad Med **18** 263 1942

64 Harrison H E and Darrow D C Renal Function in Experimental Adrenal Insufficiency Am J Physiol **125** 631 1939

65 (*a*) Loeb [63] (*b*) Harrison

66 (*a*) *Darrow* [28] (*b*) *Ferrebee J W Parker D Carnes W H* Gerity M K Atchley D W and Loeb R F Certain Effects of Desoxycorticosterone Development of Diabetes Insipidus and Replacement of Muscle Potassium by Sodium Am J Physiol **135** 230, 1941 (*c*) *Selye H* and Hall, C E Production of Nephrosclerosis and Cardiac Hypertrophy in Rat by Desoxycorticosterone Acetate Overdosage Am Heart J **27** 338 1944 (*d*) Knowlton A I Loeb E N Stoerk H C and Seegal H C Desoxycorticosterone Acetate Potentiation of Its Activity by Sodium Chloride J Exper Med **85** 187 1947

from 10 to 110 millimols for chloride and from 10 to 80 millimols for potassium.[69] The daily losses in severe infantile diarrhea are about 250 grams of water 16 millimols of sodium 11 millimols of chloride and 8 millimols of potassium per day. In adults cholera, severe diarrhea and dysentery probably lead to proportional losses. Sprue and celiac disease do not produce as severe losses of electrolyte except during periods of exacerbation. Practically all types of diarrhea tend to produce greater relative losses of sodium and potassium than of chloride. The result is a type of metabolic acidosis in which changes in the composition of intracellular fluids play an important role which has already been discussed.

Gamble and associates[71] and Darrow[72] described a rare type of congenital anomaly of intestinal absorption leading to obligatory watery stools containing more chloride than sodium. The patients had continual metabolic alkalosis and deficits of both chloride and potassium. Recent experiments indicate that diarrhea in which the stools contain more chloride than sodium develops in rats subjected to potassium deficiency.[73] Albright and Gardner have seen a similar development in an adult, which suggests that a change in intestinal absorption leading to stools containing more chloride than sodium may result when pronounced deficit of potassium develops.[74]

In the discussion of the balance of water and electrolyte, it is necessary to point out that balances of water and electrolyte within the body affect the amount of water and electrolyte available for expenditure. If there is an increase in extracellular fluids owing to formation of edema or exudates sufficient sodium and chloride must be retained to preserve the composition of extracellular fluids. When such fluids are excreted a corresponding amount of sodium and chloride is released in order to preserve extracellular concentration. These facts must be borne in mind in estimating the requirement of water and electrolyte. There is such a small amount of water and electrolyte in the body that can

71 Gamble, J L., Fahey K. R. Appleton, J E., and MacLachlan, E. A. Congenital Alkalosis with Diarrhea, J Pediat. 25 509 1945

72 Darrow D. C. Congenital Alkalosis with Diarrhea, J Pediat. 25 219 1945.

73 Gardner L. I. MacLachlan, E. A. Terry M. L., and Butler A. M. Chloride Diarrhea and Systemic Alkalosis in Potassium Deficiency Federation Proc. 8 201 1949

74 Albright, F., and Gardner L. I. Personal communication to the authors.

diarrhea, escape of gastrointestinal fluids through fistulas and aspiration from catheters introduced into the stomach and upper intestines The approximate losses may be estimated from the volumes and composition of the fluids lost Figure 5 shows the average concentrations of certain gastrointestinal fluids The volumes may be measured but usually can only be estimated approximately The losses determine the tissue deficits

As the chart shows, the gastric juice contains relatively more chloride than sodium and appreciable amounts of potassium As excreted by the chief cells the chloride concentration is somewhat higher than the concentration of sodium in serum[68] The gastric contents are the result of the mixture of the acid excretion of the chief cells with neutral or slightly alkaline secretions of other cells The amounts of each kind of secretion are so variable that gastric contents may contain considerably more chloride than sodium or more sodium than chloride Loss of acid gastric juice leaves the body with a relative excess of sodium available to form bicarbonate in extracellular fluids This type of alkalosis is typical of pyloric obstruction[69] In the vomiting of renal failure and as a result of certain infections, the fluid is not acid and may produce no change in acid base equilibrium or even acidosis In certain cases of vomiting in children typified by periodic vomiting acidosis results not only because the fluid lost is not highly acid but because starvation leads to nondiabetic ketosis[70] High intestinal obstruction and the loss of fluids through catheters introduced into the upper intestinal tract after operative procedures produce alkalosis because the amount of gastric fluid removed is greater than the amount of the intestinal juices

The stools in diarrhea vary widely in composition In some patients the electrolyte concentrations are so small that little decrease in body electrolyte develops despite the loss of large volumes of water in the stools In other patients the stools contain so much water and electrolyte that the tissues are rapidly depleted of both water and electrolyte The concentrations per kilogram of stools vary from 12 to 90 millimols for sodium

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68 Gilman A and Cowgill G R Osmotic Relation Between Blood and Gastric Juice Am J Physiol **103** 143 1933

69 Gamble J L and Ross S G The Factors in the Dehydration of Pyloric *Obstruction* J Clin *Investigation* **1** *403 1925*

70 Darrow D C and Cary M K A Clinical and Chemical Study of Non Diabetic Ketosis with Acidosis J Pediat **6** *676 1935*

appearance of systolic murmurs, (7) increased pulse pressure with Corrigan pulse, and (8) elevated venous pressure and signs of cardiac failure. The paralysis of the diaphragm and abdominal muscles and the functional disturbances of the myocardium account for the major clinical signs and symptoms.[16]

The electrocardiographic changes have received considerable study.[6a, b] While the changes are not absolutely specific, their reversal accompanying restoration of the concentration of potassium in serum indicates that they are related to serum potassium concentration. The changes which have been attributed to abnormal serum potassium are illustrated diagrammatically in figure 6. The following changes accompanying low concentrations of potassium in serum should be noticed: (1) slightly prolonged Q-T interval, (2) decreased height and inversion of the T waves, (3) rounded and prolonged T waves, (4) depression of the S-T segment and (5) possible inversion of the P waves, extrasystoles and auriculoventricular block. The precordial lead CR_4 has been found the most useful in measuring the Q-T interval. The height of the T waves has been found to be influenced by the p_H, by the partial pressure of carbon dioxide and by the concentration of potassium in serum. The electrocardiographic changes correlate only approximately with the decrease in concentration of potassium in serum.

Physiologically significant decrease in the concentration of potassium in serum may occur without characteristic signs or symptoms. Since it is not known how often or under what circumstances low concentrations of potassium in serum lead to anatomic lesions of the heart nor when serious symptoms may develop, decrease in the concentration of potassium in serum should be suspected in those conditions known frequently to be accompanied by deficiency of potassium or decrease in serum potassium concentration or both. Flame photometry has made the measurement of serum potassium a practical clinical examination. The finding of a low concentration of potassium in the serum confirms the diagnosis of low serum potassium but low serum potas-

6 (*a*) Nadler, C. S.; Bellet, S., and Lanning, M.: Influence of Serum Potassium and Other Electrolytes on the Electrocardiogram in Diabetic Acidosis, Am. J. Med. [illegible]:838, 1948. (*b*) Frenkel, M.; Groen, J., and Willebrands, A. F.: Low Serum Potassium Level During Recovery from Diabetic Coma, Arch. Int. Med. **80**: 728 (Dec.) 1947. (*c*) Tarail, R.: Relation of the Abnormalities in Concentration of Serum Potassium to Electrocardiographic Disturbances, Am. J. Med. **5**: 828, 1948.

safely be used for obligatory expenditure that small losses lead to symptoms of dehydration The dangers of dehydration have been sufficiently emphasized so that physicians do not knowingly call on body reserves to meet obligatory expenditure It is not so generally realized that expansion of body fluids may leave the rest of the body with insufficient water and electrolyte to cover obligatory expenditure and to provide adequate quantities of water and electrolyte for the renal and circulatory systems Burns exposure to cold extensive trauma inflammatory reactions and tourniquet injury [75] produce extensive expansions of fluids at the site of injury The fluid accumulated resembles extracellular fluids and the localization of water and electrolyte has the same effect as loss of extracellular water and electrolyte [8]

Accompanying the circulatory changes of tissue injury, potassium may be lost from the cells and replaced by sodium [28] The decrease in extracellular sodium produces acidosis which is further aggravated by changes in renal function dependent on the lack of water and electrolyte available for renal and circulatory functions Part of the benefit of sodium chloride therapy in shock is dependent on the changes in the cells and the obligatory expansion of extracellular fluids that is taking place

IV CLINICAL AND ELECTROCARDIOGRAPHIC DISTURBANCES ACCOMPANYING HYPOKALIEMIA

Certain symptoms and signs and electrocardiographic changes are known to be accompanied by low concentrations of potassium in serum and to be abolished by the restoration of the normal concentration The following signs and symptoms have been observed (1) weakness and hypotonia of the skeletal muscles progressing to frank paralysis (usually the paralysis of the arms and legs appears first and that of the respiratory muscles later), (2) dyspnea with gasping respirations in which the accessory muscles of respiration are invoked (3) cyanosis which is chiefly respiratory in origin but may be in part cardiac (4) abdominal distention which seems to be dependent on atonia of the smooth muscles (in experimental animals extreme deficiency of potassium produces paralytic ileus) (5) nausea and vomiting, (6) cardiac enlargement with the

75 (a) Fox [38] (b) Bl lock [48] (c) Cr smon. [7 b]

case of oliguria accompanying shock and dehydration. The increase in extracellular potassium may come from food or potassium-containing salts administered either orally or parenterally. The increase may also arise from the release of potassium from the cells caused by the catabolism of cellular structures or the release of cellular potassium which accompanies anoxia or other disturbances in cellular metabolism. It is difficult if not impossible, to produce potassium intoxication by the oral administration of potassium salts to patients with normal kidneys and circulation. However, too rapid parenteral administration of potassium salts may produce hyperkaliemia though the occurrence of serious symptoms has never been noted in our rather extensive experience or in that of others using similar methods of parenteral administration of potassium.

In almost all the reported cases of hyperkaliemia, the concentrations of sodium in serum have been low. Some of the symptoms and electrocardiographic changes may be related to the abnormal ratio of potassium to sodium. The low concentration of serum sodium certainly contributes to the circulatory and renal failure in many instances.

The treatment consists of stopping the intake of potassium, retarding the rate of release of potassium from the cells, promoting the return of extracellular potassium to the cells and increasing the excretion of potassium by the kidneys. Intravenously administered glucose will retard the catabolism of protein which leads to release of potassium from the cells in the fasting patient. It also promotes the taking up of potassium from the extracellular fluids by the formation of glycogen and perhaps by restoring certain cellular functions. Hypertonic sodium chloride solution is indicated particularly when the serum is hypotonic since it will improve the circulation and the renal function. The intravenous injection of calcium salts seems to be indicated on physiologic grounds but has been found to be of only transient benefit.

VI THERAPEUTIC APPLICATIONS

Fluid therapy should be based as far as possible on an estimation of the changes in tissue composition and the rate of expenditure of water and electrolyte. In addition to evidence of dehydration or edema obtained from the physical examination, the direction of the

sium does not develop in all forms of deficiency of potassium in the body as a whole Consideration of the contribution of hypokaliemia and potassium deficiency to the symptoms is especially important since patients likely to have disturbances in body potassium usually have other disorders which may mistakenly be considered adequately to explain the signs and symptoms The treatment of this condition consists in the oral or parenteral administration of potassium salts

V CLINICAL AND ELECTROCARDIOGRAPHIC DISTURBANCES ACCOMPANYING HYPERKALIEMIA

Certain signs and symptoms and electrocardiographic changes develop when the serum potassium concentration is elevated and are reversed if the serum potassium returns to normal The following signs and symptoms have been observed in hyperkaliemia (1) listlessness and mental confusion, (2) numbness and tingling of the extremities with a sense of weakness and heaviness of the legs, (3) cold gray pallor, (4) bradycardia and occasionally totally irregular rhythm, (5) peripheral vascular collapse with diminished quality of the heart sounds and low blood pressure, (6) in a few patients with uremia a rapidly ascending flaccid paralysis without involvement of the trunk head or bladder, and (7) cardiac arrest

The electrocardiographic abnormalities correspond roughly to the degree of elevation of serum potassium concentration The changes are illustrated diagrammatically in figure 6 At concentrations of 6 5 to 7 8 millimols of potassium per liter alterations in the T wave begin to appear These alterations are almost always present when the potassium level is above 8 millimols per liter Heart block appears above about 10 millimols per liter The sequence of changes with increasing concentrations of serum potassium is (1) appearance of peaked T waves (2) increased duration of QRS complex, (3) increased duration of the P R interval leading to auricular standstill, (4) biphasic curve with progressive delay in ventricular conduction and (5) total arrhythmia progressing to cardiac arrest [77]

Hyperkaliemia arises almost exclusively when renal excretion is greatly diminished because of renal dis

77 (*a*) Nadler (*b*) Marchand J F and Finch C A. Fatal Spontaneous Potassium Intoxication in Patient with Uremia Arch Int. Med 73 384 (May) 1944 (*c*) Finch C A Sawyer C. G and Flynn J M Clinical Syndrome of Potassium Intoxication Am J Med 1: 337 1946

frequently given by hypodermoclysis, this practice is seldom desirable since 5 per cent glucose is irritating locally and immobilizes water and electrolyte for a period of seven or more hours [22] The immobilization of water and electrolyte can produce all the signs and symptoms of dehydration One part of isotonic sodium

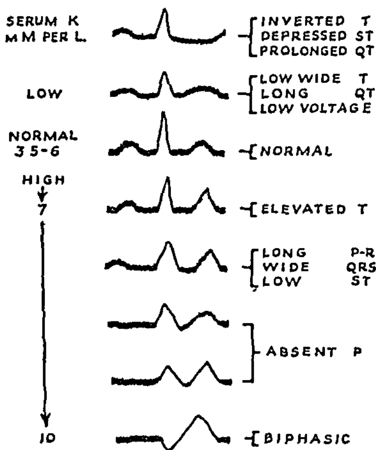


Fig 6—Diagrammatic representation of the changes in the electrocardiogram associated with the changes in the concentration of potassium in serum.

chloride solution added to one or two parts 5 per cent glucose has few of these objections The rate of intravenous injection should not be greater than the body can handle The *slow injection of 5 to 10 per cent* glucose in amounts which cover water expenditure does not give more glucose than can be metabolized One hundred cubic centimeters of 5 per cent glucose

change in body water may be obtained from the body weight Evaluation of the acid base equilibrium requires the determination of serum bicarbonate and p_H, which should always be evaluated in relation to the respiratory rate and depth in order to estimate the efficiency of the exchange of gases in the lungs The serum concentrations of bicarbonate plus chloride, or, more reliably the concentration of sodium shows whether fluids are hypotonic or hypertonic The concentration of potassium is valuable but alone does not determine the existence of potassium deficiency When the therapy is followed from day to day the body weight is the most reliable evidence of change in body water and should be determined accurately in adults as well as infants Measurement of the volume of urine and other excreta is often necessary in making the decision as to the kinds and amounts of fluid to be administered Restoration of the circulation in shock is essential Since shock cannot be recognized with certainty by clinical observations, treatment with transfusion of blood or infusion of plasma should be given to many patients with disturbances of water and electrolyte who might recover without these therapeutic measures

The following general principles are used in planning therapy (1) treatment of shock by infusion of solutions replacing the deficit of electrolyte and blood transfusions or infusions of plasma or human plasma albumin (2) replacement of deficit of electrolyte with solutions which provide for the restoration of sodium, potassium chloride and phosphate as indicated by the estimated deficiencies (3) provision of water and electrolyte to cover the expenditure as calculated from the metabolic rate and abnormal losses (4) appropriate therapy to overcome abnormal metabolic reactions as in diabetes adrenal insufficiency renal failure and diarrhea and (5) avoidance of disturbances produced by the solutions used According to the chief purpose for which they are appropriate the various solutions may be grouped in four categories (1) provision of water (2) replacement of electrolytes (3) maintenance of nutrition and (4) prevention and treatment of shock

FLUIDS APPROPRIATE FOR FURNISHING WATER

Parenteral water is most effectively given by the intravenous injection of a 5 or 10 per cent solution of glucose in water Although 5 per cent glucose is

excessive amounts of sodium bicarbonate or sodium lactate, particularly if deficit of potassium is not replaced, may produce alkalosis and tetany It has been shown that signs and symptoms of tetany do not occur when the concentration of calcium in serum is at levels usually accompanied by tetany if the concentration of potassium is abnormally low Restoring the level of serum potassium to normal may induce tetany if the serum calcium remains low For this reason attention must be paid to the possibility of low concentrations of both calcium and potassium occurring in the same patient [8] Ionic solutions containing chiefly sodium and chloride produce no toxic ionic effects and diffuse rapidly out of the vascular compartment into the interstitial fluids They may be injected as rapidly as 30 ml per kilogram of body weight per hour except when there are cardiac or other contraindications to rapid infusion

The solution containing sodium chloride sodium lactate and potassium chloride developed by Darrow (called 'K lactate) contains sodium and chloride in the ratio of interstitial fluid together with an amount of potassium which is unlikely to raise the serum concentration of potassium to toxic levels when the solution is injected over a period of four or more hours in amounts which give appropriate amounts of sodium and chloride It contains 4 0 Gm of sodium chloride 2 7 Gm of potassium chloride and 52 ml of molar sodium lactate per liter The concentration of potassium is about ten times as great as that of serum In order to avoid the danger of potassium intoxication it should be injected, preferably subcutaneously over a period of four or more hours for the dose appropriate for one day Theoretically and practically it is not necessary to give more than 80 ml per kilogram in order to replace a maximum deficit of extracellular electrolyte The deficits of potassium are often so large that they cannot be restored parenterally in less than six days because of the dangers of more rapid parenteral administration of potassium and because administration of more potassium does not restore cell deficits more rapidly [79]

K lactate may be injected slowly into the veins or subcutaneously If given intravenously one part of the K lactate solution should be diluted with two or three

78 Deleted on proof

79 Wallace W M Metcalf J, and Holliday M A Studies on the Efficiency of Electrolyte Repair in Dehydration Proc Soc. Ped. Research 1949

per 100 calories metabolized supplies sufficient glucose to produce maximal protein sparing and to eliminate ketosis and achieve the conservation of extracellular fluid due to glucose[5, 6] Ten per cent is as high a concentration as is well tolerated by the veins over long periods Glucose solutions should be made up in water for most purposes In planning the total fluid intake for twenty four hours, it is appropriate to add glucose in water to isotonic sodium chloride solution and other solutions containing electrolyte However the electrolyte should be administered in quantities appropriate for replacement of deficits and expenditure of electrolyte Since isotonic sodium chloride solution requires about one fourth to one half of its water to excrete the salt in the urine sodium chloride solutions should not be regarded as a means of supplying more than a minor part of the water requirement. Except during the first twenty-four hours of treatment when a large deficit of electrolyte is being replaced, the total mixture given over a period of twenty-four hours should not contain more than one-third isotonic electrolyte.

FLUIDS FOR REPLACEMENT OF ELECTROLYTE

Isotonic sodium chloride solution is the basic solution in this category because it appropriately contains the principal ions of extracellular fluids and is easily sterilized It contains relatively more chloride than extracellular fluids A mixture of two or three parts isotonic sodium chloride solution and one part isotonic (sixth molar) sodium lactate solution more nearly resembles interstitial fluid Hartmann s lactated Ringer s solution and a suitable mixture of sodium chloride and sodium bicarbonate imitate interstitial fluid quite closely *Isotonic* sodium lactate injection is given primarily to replace a deficit of sodium relatively greater than the *deficit of chloride Deficit of sodium is probably never* greater than 12 ml of molar sodium lactate per kilogram of body weight or the equivalent amount of sodium *bicarbonate (1 Gm) Seventy milliliters per kilo*gram of body weight is therefore the maximum dose of sixth molar sodium lactate for immediate replacement *over a short period* It is probably *seldom if ever* advisable to use this much sodium lactate or the equivalent amount of sodium bicarbonate but larger doses may be required over a period of several days if sodium loss continues The treatment of metabolic acidosis with

of fats is still experimental Amino acids and protein hydrolysates may supply the protein needs when combined with glucose About 2 Gm per 100 calories metabolized is the usual amount given in twenty four hours, that is about 1 Gm per kilogram in adults and 2 5 Gm per kilogram in infants The amino acids are usually combined with glucose, water and electrolyte so as to meet all the expenditure of water and electrolyte. A mixture of 2 Gm of amino acids in 150 ml of 10 per cent glucose yields about 68 calories while 2 Gm in 225 ml of 10 per cent glucose yields 100 calories These units are appropriate amounts to be given per estimated 100 calories metabolized Both supply the water requirement, but only the latter meets the caloric expenditure.

SOLUTIONS FOR THE PREVENTION OR TREATMENT OF SHOCK

Compatible whole blood in amounts of 30 ml per kilogram of body weight for an infant to half that amount for an adult is in general the most effective agent for the prevention or treatment of shock Whole blood is indicated to sustain red cells and plasma volumes and to add to the oxygen-carrying capacity of the vascular compartment The red cells have important functions in carbon dioxide transport and in the buffer effect of hemoglobin In dehydration due to loss of electrolytes the effectiveness of the appropriate electrolyte solution is enhanced if blood (or plasma) is also administered [84] The prejudice against giving whole blood in dehydration is unfounded experimentally and when accompanied by proper quantities of water and electrolyte solutions the administration of whole blood has clinically demonstrated its value [82]

Plasma, either separated from cells or reconstituted from lyophilized plasma, has the advantage of greater availability but is somewhat inferior to whole blood except in a few conditions Because of the dangers of hepatitis irradiated plasma or plasma derived from a single donor is much safer than pooled plasma Human serum albumin given in its concentrated form has a greater effect on the oncotic pressure in the vascular compartment than plasma or whole blood and does make

82 Powers G F A Comprehensive Plan of Treatment for So-Called Intestinal Intoxication of Infants Am. J Dis Child 32 232 (Aug) 1926

parts of 5 or 10 per cent glucose in water Butler and Talbot [80] have advocated a solution for intravenous use that is *similar to "K lactate" diluted with two parts* 5 or 10 per cent glucose in water This solution contains 5 *millimols* of phosphate per liter and is appropriate for diabetic coma and may have advantages in diarrhea and other conditions Since acidosis is usually dependent on loss of potassium as well as sodium solutions containing potassium as well as sodium salts are practically always indicated in acidosis In the acidosis of diarrhea, it has seldom seemed necessary to administer sodium bicarbonate or sodium lactate in addition to that contained in the 'K lactate' solution Since the dehydration of diarrhea probably presents as severe a depletion of electrolyte as is found *in any condition, this solution should be equally effective* in other types of acidosis (such as diabetic acidosis and nondiabetic ketosis) *Potassium containing solutions* should not be used in Addison's disease and should be used only in appropriate cases of renal acidosis

In alkalosis with potassium depletion as well as relative deficit of chloride in relation to sodium theoretic considerations indicate that a mixture containing about 6 Gm of sodium chloride and 2 7 Gm of potassium chloride per liter should be more effective than isotonic sodium chloride solution Such a solution may be injected subcutaneously at a slow rate but should be diluted with two or three parts 5 or 10 per cent glucose in water if injected into the veins N K Ordway informs us that he has successfully used higher concentrations of potassium and equal parts of isotonic sodium chloride and potassium chloride Ammonium *chloride has been injected intravenously in severe* alkalosis [81] While this therapy is effective in hastening the *restoration of the concentration of bicarbonate in serum* it fails to correct the deficiency of potassium which is the cause of the ineffectiveness of isotonic sodium chloride solution in refractory alkalosis

FLUIDS FOR PARENTERAL FEEDING

Parenteral feeding is limited to vitamins and *solutions* of glucose and amino acids since intravenous injection

80 Butler, A M, and Talbot N B Parenteral Fluid Therapy in Diarrheal Disease Am J Dis Child **72** 481 (Oct) 1946

81 *Zindel H A* Rhoads J E and Ravdin I S *Use of Intravenous* Ammonium Chloride in Treatment of Alkalosis Surgery **14** 728 1943

would need between 1,600 and 2,250 ml In addition to the minimal requirement of water and electrolyte, patients with abnormal losses of water sodium chloride and potassium may require treatment for shock, replacement of the deficits and provision for continuing losses of water and electrolyte The fluids used will vary considerably according to the initial serum electrolyte concentrations the disturbances in acid base equilibrium, the age and the amount and kind of abnormal losses

When there are profound circulatory disturbances and shock, the initial treatment should be infusion of 20 to 30 ml per kilogram of body weight of a solution containing chiefly sodium chloride If there is metabolic acidosis a mixture of one part isotonic sodium lactate and two parts isotonic sodium chloride solution is better than sodium chloride alone though the latter is usually effective Blood transfusions should follow as soon as possible in severe cases Plasma may be used in the place of blood and sodium chloride when blood is not available In metabolic alkalosis the same initial plan of therapy is followed except that isotonic sodium chloride solution is the appropriate solution In both acidosis and alkalosis the replacement of potassium as well as of sodium and chloride may be started as soon as the circulation has improved and urine is being formed

The deficit of extracellular electrolyte is seldom greater than one third of the normal content even in the most severe dehydration Hence with babies with severe losses of water and electrolyte the deficiency of sodium and chloride is restored by 80 ml per kilogram of body weight of the appropriate solution containing these ions at about physiologic concentration Seventy milliliters per kilogram suffices for adults Smaller amounts are required in less severe cases The deficit of water is replaced by the appropriate sodium chloride solution together with the water given to cover obligatory expenditure The deficits of potassium may reach half the total muscle content in experimental animals or about 25 millimols per kilogram of body weight Probably 15 millimols of potassium per kilogram of body weight is encountered in patients A large deficit probably cannot be replaced in less than four to six days since the cells do not repair this deficiency rapidly Although as much as 7 milli

it possible to supply relatively large amounts of serum albumin to patients The following paragraphs will illustrate how certain situations are met when patients are unable automatically to meet fluid requirements

The need to administer all fluids parenterally arises frequently in all fields of medicine but particularly in the postoperative care of surgical patients Since only sodium chloride solutions are well tolerated when injected subcutaneously, all or a large part of the water requirement must be given by vein The most convenient method of injection is infusion of appropriate solutions through intravenous drip The solutions required should be carefully calculated to fulfil the needs for twenty four hours, and the rate of injection should be regulated with due consideration for the comfort of the patient and the dangers of too rapid injection When there are no abnormal losses or shock the requirement of electrolyte is small probably not over 10 to 20 ml of isotonic sodium chloride solution per 100 calories metabolized After operative procedures the kidneys tend to conserve both water and sodium chloride[83] For this reason it usually is desirable to limit the intake of water and salt to the requirements for low urine losses Furthermore adding sodium chloride to glucose solutions leads to retention of sodium and excretion of potassium[84] The amount of electrolyte released by the catabolism of tissues during fasting may be sufficient to cover obligatory expenditure in many patients Five grams of glucose per 100 calories metabolized will induce maximal sparing of protein Further protection of body protein can only be obtained by the addition of 2 to 3 Gm of amino acids together with sufficient glucose to cover the caloric expenditure The calculation of the total fluid requirement is indicated in the previous section in which the factors controlling water expenditure are discussed For each 100 calories metabolized water requirement lies between 90 and 125 ml Ten to twenty ml may be given as isotonic sodium chloride solution or as K-lactate' and the rest as 5 or 10 per cent glucose in water Two grams of amino acids may be added to the fluid in appropriate cases A 5 Kg infant metabolizing 500 calories would require between 450 and 625 ml of a suitable mixture while an adult

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83 Cooper D R Iob V and Coller F A. Re p nse to Parenteral Cluco e of Normal K dneys and Kidneys of Postoperative Pat ents Ann Surg **129** 1 1949

would need between 1,600 and 2 250 ml In addition to the minimal requirement of water and electrolyte patients with abnormal losses of water, sodium, chloride and potassium may require treatment for shock replacement of the deficits and provision for continuing losses of water and electrolyte The fluids used will vary considerably according to the initial serum electrolyte con centrations the disturbances in acid base equilibrium, the age and the amount and kind of abnormal losses

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equivalents of potassium per kilogram has been given parenterally, 3 milliequivalents (0 22 Gm of potassium chloride) per kilogram per day is as much as is safe and efficiently utilized

In acidosis, deficit of extracellular electrolyte is usually satisfactorily replaced by a mixture of one part isotonic sodium lactate and two parts isotonic sodium chloride solution Since, in most instances, acidosis is accompanied by potassium deficit, 'K lactate" usually is more appropriate In diabetes and perhaps in other conditions the addition of about 0 7 Gm potassium dihydrogen phosphate per liter as advocated by Butler and Talbot is advantageous Isotonic sodium chloride solution is usually effective in alkalosis, but if vomiting has been prolonged or postoperative suction is being carried out the solution containing 6 Gm of sodium chloride and 2 7 Gm of potassium chloride is indicated Any of these solutions may be injected subcutaneously but if given intravenously the solutions containing potassium should be diluted with two or three parts of 5 or 10 per cent solution of glucose in water Potassium containing solutions should be given over a period of four or more hours in either instance It given subcutaneously appropriate amounts of glucose in water should be injected intravenously unless sufficient water is taken by mouth After replacement of the initial deficit of water and electrolyte, the continuing losses can be replaced and the obligatory expenditure covered by administration of 125 to 150 ml per 100 calories metabolized of a mixture of one part of the appropriate electrolyte solution and two or three parts 5 or 10 per cent glucose in water As long as there is deficit of water and electrolyte, oral feeding is likely to induce vomiting and may aggravate diarrhea After the initial deficits of water and electrolyte are replaced solutions containing water and electrolyte are often well tolerated orally and may be given before food can be ingested

In infantile diarrhea milk feeding increases the loss of water and electrolyte in the stools and should be omitted for twenty four hours or until one is assured that milk will not lead to vomiting or greatly increase the bulk of the stools Food should be started by giving 10 to 20 calories per kilogram of a suitable milk mixture diluted with sufficient water to cover a high rate of expenditure (150 ml per kilogram) With the

total intake of water kept constant the proportion of milk should gradually be increased over a period of five to twelve days until full caloric feeding is given (100 calories per kilogram) One gram of potassium chloride should be added to each day s food when the milk mixture is providing less than 70 calories per kilogram per day Most infants with severe dehydration in diarrhea should receive transfusions Provision for more sodium lactate or bicarbonate than is obtained from K lactate is seldom if ever, necessary to overcome the acidosis in infantile diarrhea Adults may be treated similarly by basing the amounts of fluid for expenditure on the estimated caloric production

Treatment of diabetic acidosis requires the proper replacement of deficits of water sodium chloride potassium and phosphate as well as the administration of insulin Blood transfusions are seldom necessary K lactate' fortified with phosphate is indicated for replacement of electrolyte Glucose in water is indicated to provide water for obligatory water expenditure as long as fluid cannot be taken orally When the blood sugar is high the injection of glucose may be delayed for an hour or two until the effect of insulin injection is taking place Broth and diluted fruit juices may be taken early in diabetic acidosis and both provide considerable potassium Broth should contain sodium chloride at about one-fourth physiologic strength (2.25 Gm sodium chloride per liter)

Deficiency of sodium and chloride but not potassium develops in the patient with adrenal insufficiency A mixture of one part isotonic sodium lactate solution and two parts isotonic sodium chloride solution may be used to replace the deficit of electrolyte. Solutions containing large amounts of potassium should not be given Glucose solutions are essential for support of the blood sugar, as well as for provision of water Desoxycorticosterone acetate corrects the disturbance in renal function but does not replace the other functions of the adrenal glands Large doses of cortical extract are the only means of fully replacing the adrenocortical functions At present the adrenocortical extracts do not contain sufficient active steroids completely to fulfil the functions of the adrenal glands except in large amounts and at prohibitive costs

Most patients with gastric alkalosis are satisfactorily

treated with isotonic sodium chloride solution However, potassium deficiency will have developed in a number who will require both potassium and sodium chloride Surgical patients subjected to duodenal drainage require replacement of potassium as well as sodium chloride The possibility of potassium deficiency as the primary cause of metabolic alkalosis should always be borne in mind This phenomenon is encountered in certain patients with adrenocortical tumors patients receiving desoxycorticosterone acetate and sodium chloride patients with chronic diarrhea who take little food and patients who have recovered from acidosis accompanied by potassium deficiency and who were treated with sodium salts while they were unable to take adequate amounts of food If electrolyte concentration is high little or no electrolyte solution may be required Fluids should consist chiefly of intravenously administered glucose in water

The treatment of acidosis seldom requires fluids containing more sodium bicarbonate or sodium lactate than is contained in one part isotonic sodium lactate solution and two parts isotonic sodium chloride solution or K lactate (80 ml per kilogram for the most severe types) If insufficient water is given when isotonic sodium chloride solution alone is used acidosis may be aggravated particularly if there is deficit of potassium as well as of sodium and chloride If sodium lactate is given in severe acidosis the amount should be about 5 to 10 ml of molar sodium lactate per kilogram This may be given intravenously at third molar or fourth molar concentration if one is dealing with hypotonic dehydration In hypertonic dehydration sixth molar is the best concentration for intravenous injection Sodium lactate injection may be given subcutaneously after dilution to sixth molar concentration

The treatment of edema is directed primarily toward the factors producing edema such as the low concentration of albumin heart failure and renal disease Purified low sodium albumin is the most effective diuretic in patients with low serum albumin When edematous patients have low electrolyte concentration renal and circulatory functions may sometimes be improved by restoring the sodium concentration with the intravenous injection of 2 or 3 per cent solution of sodium chloride However restriction of salt is advantageous in most types of edema On the other hand if water intake

has been restricted Schemm[84] points out that diuresis is most likely to occur when the intake of water is increased, salt restricted and the diet yields a neutral or acid ash To be effective, Schemm emphasizes that the water intake must be extremely high (4 000 ml in adults) It is probable that the effectiveness of Schemm's treatment is dependent on the avoidance of conditions leading to a concentrated urine Acidosis in edematous nephritic patients may require the oral or intravenous administration of sodium bicarbonate or lactate Such treatment is instituted with reluctance since the intake of sodium bicarbonate aggravates the edema.

SUMMARY

The first two sections discuss the relation of the vascular to the extracellular compartments and the composition of the body as a whole The changes in composition taking place in dehydration acidosis and alkalosis the changes in electrolyte concentration and the changes in the volume of extracellular fluids are described Emphasis is placed on alterations in intra cellular as well as extracellular fluids Changes in the relation of body sodium potassium and chloride are related to the acid base equilibrium as well as to changes in hydration and water distribution The third section discusses the factors controlling expenditure of water and electrolyte Normal water expenditure is closely correlated to heat production and urinary concentration Sweat volume is related to heat balance The abnormal losses occurring in the urine stools vomitus and other gastrointestinal secretions are described The fourth and fifth sections describe the symptoms and diagnosis of hypokaliemia and deficiency of potassium and hyperkaliemia The sixth section discusses fluid therapy in the light of the concepts developed in the previous sections It is pointed out that the aim of fluid therapy is to restore and maintain the normal composition of the tissues

84 Schemm F R High Fluid Intake in the Management of Edema Especially Cardiac Edema Details and Basis of the Regime Ann. Int Med. 17:952 1942

CHAPTER XXI

DEFICIENCIES OF THE FAT-SOLUBLE VITAMINS

JOHN B YOUMANS

VITAMIN A

In addition to the general limiting effect on growth common to all nutrients vitamin A seems to affect almost exclusively the mechanism of the adaptation of vision to dim light (dark adaptation) and the health and integrity of the epithelium The functional and structural changes resulting from a deficiency of this vitamin constitute the manifestations of the deficiency disease

Dark Adaptation —The adaptation of vision to dim light principally a function of the retinal rods requires an adequate supply of vitamin A (vitamin A_1) The process depends on the presence of an adequate amount of visual purple (rhodopsin) Vitamin A with a protein forms visual purple Visual purple, or rhodopsin, is reversibly broken down in bright light to retinene which in turn is reconverted to vitamin A_1 by a reaction involving reduced cozymase as a co-enzyme Recent studies indicate a complicated process possibly involving two other vitamins niacin acid and vitamin E as well as proteins [1] The continuous process of breakdown and regeneration while obviously a reversible process is not completely so and is accompanied with some loss of vitamin A requiring a supply for replacement Without an adequate supply the formation of visual purple fails and poor dark adaptation (night blindness) results

Poor dark adaptation (night blindness or nyctalopia) has been known for centuries in circumstances now known to be related to deficient intakes of vitamin A It occurs also under conditions interfering with the absorption, storage and utilization of vitamin A and carotene or the conversion of the latter to vitamin A

1 Wald G Th En ymat c Reduct on of the Retinenes to the Vitamins A Science 109 48 1949

Such conditions include gastrointestinal disease, sprue and disease of the liver

Slight night blindness is not recognizable except by instrumental means, even by the subject Mild complaints include difficulty in reading, sewing or detecting objects in dim light and stumbling in the dark particularly on sudden changes from bright to dark There may also be undue sensitivity to sudden bright light In severe cases the subject is so blind as to be incapacitated in dim light

Epithelium —Although vitamin A deficiency affects the epithelium in many sites certain places are for one reason or another of greater clinical importance than others They are the eyes the skin the upper parts of the respiratory passages the bronchi and perhaps the genitourinary tract These are of particular importance either because their location makes them readily observed or because the symptoms they produce are particularly important

Eyes The changes in the epithelium of the eye involve particularly the scleras, the corneas and the tear glands and ducts The other glands and the conjunctivas are involved to a lesser extent Perhaps the earliest noticeable change is functional decreased tearing although it is possible that this is preceded by a brief stage of increased lacrimation The characteristic conjunctivitis of vitamin A deficiency, however, is a dry conjunctivitis This is accompanied with itching and burning and perhaps, some redness of the conjunctivas Follicular conjunctivitis and granular lids have been reported as a result of the deficiency this stage has been called prexerosis Another early change is cornification of the epithelium of the corneas and scleras particularly the latter This can be detected in stained smears obtained from corneal or scleral scrapings, the epithelial cells showing the characteristic staining reactions and structural changes of keratinization or cornification As the disease progresses the metaplasia, cornification and desquamation of the ocular epithelium increases Secretion of tears ceases On the scleras there is a piling up of epithelium to form localized spots' areas of thickening with a decreased translucency When fully developed they may become Bitot's spots silvery or pearly raised usually triangular, areas, with the base toward the cornea and as a

rule, lateral to the cornea on the equator of the eye There may be a pigmented background The scleras take on a greasy appearance and wrinkle easily, at the same time becoming generally more opaque and lusterless There is edema of the cornea and infiltration with leukocytes at first in localized areas, later becoming diffuse and involving the entire cornea the latter change often appearing precipitously At about this point, or somewhat before the stage known as xerophthalmia or keratomalacia is present, and progression of the disease is often followed by secondary infection (corynebacterium xerose is a common invader) panophthalmitis hypopyon and often loss of the eye Vision is impaired from the beginning of corneal keratinization and clouding Microscopically there is metaplasia followed by atrophy and desquamation of the epithelium of the tear glands and ducts as well as the cornification of the scleral and corneal epithelium

In addition to these changes, Kruse[2] has described what he considers still earlier or milder changes, mainly in the subepithelium detectable only with magnification and proper illumination (slit lamp and suitable microscope) Others[3] however, believe these to be senile and presenile changes or the effect of physical or other irritants such as wind and dust, rather than the result of vitamin A deficiency An important criticism of Kruse s theory is the failure of the lesions to clear, despite administration of large doses of vitamin A over long periods In animals[4] the response is rapid and complete It is true that the lesions may be more chronic in man but it is difficult to accept failure of cure in so slight a lesion as consistent with Kruse s hypothesis Elsewhere the repair microscopically as well as grossly is relatively rapid In rabbits the corneal epithelium corneal nerve fibers and retina are not affected nor does corneal vascularization or infiltration occur In subjects with true xerosis or xerophthalmia the level of vitamin A in the blood is usually low[5] as is true experimentally

2 Kruse H D The Detection of Ocular Changes in Avitaminosis A Pub Health Rep 56: 1301 1941

3 Berliner M L Regarding the Early Detection of Avitaminosis A by Gross or Biomicroscopic Examination of the Conjunctiva Am. J Ophth 25: 302 1942

4 Mann, I Pirie A Tansley K and Wood C Some Effects of Vitamin A Deficiency on the Eye of the Rabbit Am J Ophth 28 801 1946

5 DeHass J H and Meulemans, O Vitamin A and Carotenoids in Blood Deficiencies in Children Suffering from Xerophthalmia, Lancet 1: 1110 1938

Recovery following treatment may be incomplete and scars are left if the damage has passed beyond the reversible stage This occurs fairly early in the case of the cornea, and corneal scars are not uncommon Otherwise, the eye returns to normal

Upper Part of the Respiratory Tract Changes similar to those in the conjunctiva and the lacrimal glands occur in the mucosa of the upper part of the respiratory tract, notably in the sinuses and nares The eustachian tubes and salivary glands and ducts are similarly involved The nares are of particular importance because they provide a handy source of epithelial scrapings which may be of some help in diagnosis at least in infants Such changes may favor the occurrence or at least the persistence of localized infections In the mouth and throat these same changes occur, but the normal degree of cornification at these sites makes them of little practical interest Despite some speculation on the relation of these changes and vitamin A deficiency to buccal leukoplakia no definite relationship has been established However, the presence of characteristic alterations in the salivary glands and ducts is easily shown

Bronchi The stratification cornification and desquamation of the mucosal epithelium of the bronchi, bronchioles and bronchial glands is of particular clinical importance because of their relation to atelectasis and pneumonia in infants The process is said to be the most common mechanism of death in infants dying of vitamin A deficiency[6] With the epithelial metaplasia and atrophy there is, of course, loss of cilia and decrease or cessation of bronchial secretions What part these changes may play in chronic disease particularly in chronic infections of the bronchi is not well established

Genitourinary Tract Metaplasia of the epithelium followed by cornification desquamation and replacement with stratified epithelium, undoubtedly occurs in the genitourinary tract It is questionable whether or not the leukoplakia in this area is the result of vitamin A deficiency[7]

In the renal pelvis and in the bladder such changes have been alleged to provide a nidus of desquamated

6 Blackfan K. D and Wolbach S B Vitamin A Deficiency in Infants Clinical and Pathological Study J Pediat. 3 679 1933

7 Patch F S Epithelial Metaplasia of the Urinary Tract, J A. M A 136:8 4 (March 20) 1948.

epithelium about which the desposition of mineral salts form calculi. A noninfectious vaginitis, especially in elderly women, has been attributed to the same cause.[8] Neither has been clearly established clinically. Similar changes in the epithelium of other organs, such as the pancreas, have been suspected, but attempts to link vitamin A deficiency with such conditions as fibrocystic disease of the pancreas have failed. Absence and defective formation of dentin and enamel of the teeth occur, with resulting deformities of the teeth.

Skin. Much has been written and considerable uncertainty and difference of opinion has arisen over the question of changes in the skin in vitamin A deficiencies. In part this is a reflection of the general lack of knowledge concerning cutaneous lesions in any of the deficiency states. As Wolbach points out,[9] no one has as yet been able to correlate such lesions with known functions of the skin or "the normal morphologic sequences of the epidermis and its appendages."

There can be little doubt that a characteristic dermatitis occurs as a result of vitamin A deficiency, as described in the classic papers of Frazier and Hu[10] and Loewenthal.[11] The differences of opinion and the uncertainty have occurred in part because of the designation by some writers of minor abnormalities of the skin as characteristic of vitamin A deficiency. Such changes, dryness for example, which, occurring in vitamin A deficiency, is nonspecific, occur from many other causes. Their presence, labeled as a sign of vitamin A deficiency in circumstances clearly eliminating such as a cause, has been confusing. In part such confusion has resulted from a lack of proper knowledge and understanding of various diseases and abnormalities of the skin on the part of some observers. As an example, ichthyosis, a congenital disorder of the skin unrelated to vitamin A, is confused by some with the dermatosis resulting from vitamin A deficiency.

The typical, characteristic lesion of the skin in vitamin A deficiency is the dry, horny perifollicular hyper-

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8 Simpson, J. W., and Mason, K. E.: A New Concept of Senile Vaginitis, Am. J. Obst. & Gynec. 32:125, 1936.

9 Wolbach, S. B.: Pathology in Relation to Nutritional Research, Nutrition Rev. 3:193, 1945.

10 Frazier, C. N., and Hu, C. K.: Cutaneous Lesions Associated with a Deficiency of Vitamin A in Man, Arch. Int. Med. 48:507, 1931.

11 Loewenthal, L. J. A.: A New Cutaneous Manifestation in the Syndrome of Vitamin A Deficiency, Arch. Dermat. & Syph. 28:700 (Nov.) 1933.

keratotic papule Microscopically, the papule is seen to arise from and about the pilosebaceous follicle The lumen and mouth of the follicle are enlarged and filled with a plug of dense, horny cornified desquamated epithelium arranged in concentric lamellas, often surrounding the remnant of a hair There are varying degrees of metaplasia and keratinization of the follicular epithelium, with hyperplasia of adjacent epidermal cells and hypertrophy and hyperkeratinization of the superficial epidermis There is a mild, irritative, inflammatory reaction of the cutis vera around the follicles, with little cellular infiltration There are varying grades of metaplasia and atrophy of the sebaceous glands and many may disappear Sweat glands and ducts show similar changes There is some increase in melanin about the follicles In the type described as aceneform the changes are similar and resemble the changes in acne without the cellular infiltration

The papules range in size from pinhead to 5 cm in diameter and are distributed principally on the extensor surfaces of the arms and thighs, shoulders abdomen back and buttocks in frequency in the order named The papules are conical or hemispherical and contain the central plug When the latter is expressed a gaping hole is left Hairs are short, broken off or absent There may be increased pigmentation about the papule Infection is absent in uncomplicated cases, but pustules and furuncles may be present as a complication In addition to these more characteristic lesions the skin is commonly dry and rough with a fine branny desquamation So called crackling a change resembling ichthyosis somewhat, is not in my opinion a significant observation It is most often observed on the lower leg an area infrequently involved by the papular eruption

In this country papules of large size or extensive distribution are uncommon The usual lesion is about the size of the papule of ordinary gooseflesh,' with which it may be confused unless one takes care to note the chilliness and strokes the area causing the papules to disappear Washing may lessen the eruption a natural result since the effect is to remove the heaped up dead epithelium It should not be allowed to be misleading

In certain patients a somewhat different lesion appears to be the result of vitamin A deficiency[12] This is an acne like eruption with dull red, flat or slightly conical, discrete papules of about the usual size of the acne papule The individual lesions often simulate a pustule but the whitish top, when pierced or removed, proves to be a thin scale with a raw surface but no pus underneath Significant features are the occurrence of the lesion after the patient is beyond the ordinary age at which acne occurs and a distribution of the lesions over the anterolateral surface of the arms and back, with few if any on the face or abdomen They may be found on the thighs and buttocks The skin is not dry or rough, and the lesions seem more common in those who bathe frequently An association of vitamin A deficiency with true acne has been suspected but has not been established[13] There is evidence to indicate that comedos may have a similar relationship at least in part[14]

The dermatosis of vitamin A deficiency is uncommon in children before puberty which has been related by Frazier and his associates[15] to changes in the sebaceous glands and hair which occur at that time The variability of vitamin needs at different periods of growth and development under the influence of endocrine functions and the greater demands at certain periods are important in this regard

It must be emphasized that the specificity of the skin lesions has not been established and doubt has been expressed of their relationship to vitamin A The observations and conclusions of Sullivan and Evans[16] are frequently referred to in this respect and are of particular interest because they represent what I believe is a misunderstanding of the nature of the lesions and a misinterpretation of experimental observations These

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12 Youmans J B and Corlette M B Specific Eruptions of the Skin Due to Deficiency of Vitamin A *Tr A Am Physicians* **52** *49* 1937 Specific Dermatoses Due to Vitamin A Deficiency Am J M Sc **195** 644 1938

13 Lynch F W and Cook C D Acne Vulgaris Treated with Vitamin A Arch Dermat & Syph **55** 355 (March) 1947 Straumfjord J V Vitamin A Its Effect on Acne A Study of 100 Patients Northwest Med **42** 219 1943

14 Hohmann W J and Beening G W Epidemic of Comedones and Vitamin A Deficiency *Nederl tijdschr v geneesk* **91** *1465 1947*

15 Frazier C N and Hu C K Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency Study of 207 Cases Arch Dermat & Syph **33** 825 (May) 1936 Frazier C N Hu C K and Chu F Variations in the Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty ibid **48** 1 (July) 1943

16 Sullivan M, and Evans V J Nutritional Dermatoses in the Rat XI Vitamin A Deficiency Superimposed on Vitamin B Complex Deficiency *Arch Dermat. & Syph* **51** *17 (Jan) 1945*

workers question the relation of vitamin A to the dermatosis just described on the following basis The pathogenesis of the epithelial lesions of vitamin A deficiency is assumed to be atrophy followed by metaplastic epithelial hyperkeratinization The skin is already keratinized, therefore, how can such changes occur? Sullivan and Evans support their conclusions by studies in rats dermal lesions failed to develop in rats on a diet deficient in vitamin A, but when a deficiency of B vitamins was added a thin, atrophic skin, followed later by some keratinization of the hair follicles, did develop Such an argument misses the essential point as it is often missed clinically that the lesion in man is primarily a lesion of the follicles and sebaceous sweat glands The papule is a perifollicular papule The epithelium of the hair follicles, sweat glands and sebaceous glands is not normally keratinized it becomes so The changes in the horny layer, while present, are not great or especially characteristic

The question of the relation of vitamin C to the dermatosis commonly attributed to vitamin A deficiency is more difficult Lesions of the skin, apparently identical except for hemorrhage, with those attributed to vitamin A deficiency, have frequently been described in cases of scurvy [17] This has generally been interpreted as indicating the presence of a deficiency of vitamin A and C, though some writers have considered it a manifestation of vitamin C deficiency alone This view has been strengthened and the question of the relation of vitamin A to the dermatosis considerably clouded by the development of such an eruption in human subjects with experimentally induced scurvy (hypovitaminosis C) [18] In the latter cases however as in the naturally occurring cases the papules have been hemorrhagic except in the earliest stages In typical cases of what has been thought to have been vitamin A dermatosis there has been no hemorrhage

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17 Scheer M and Keil H Follicular Lesions in Vitamin A and C Deficiencies Arch. Dermat & Syph 30 177 (Aug) 19 4

18 Vitamin C Requirement of Human Adults Experimental Study of Vitamin C Deprivation in Man A Preliminary Report by the Vitamin C Sub Committee of the Accessory Food Factors Committee Medical Research Council Lancet 1:853 1948

Perhaps the solution of this problem lies in recent observations on vitamin A deficient rats [19] These animals exhibited signs of scurvy which were relieved with massive doses of ascorbic acid Previous workers had shown lowered levels of ascorbic acid in blood and tissue in experimental animals rendered deficient in vitamin A [20] If the possibility be accepted that a deficiency of one vitamin may cause at least an effective deficiency of another, as in this instance then a deficiency of vitamin C might lead to a deficiency of vitamin A, with the development of the characteristic dermatosis which in such circumstances might have the added picture of hemorrhage In any event, it is my opinion that in many instances the dermatosis described is the result directly or indirectly, of vitamin A deficiency and should be so treated It cannot, however be considered specific or pathognomonic at present As in all but pathognomonic lesions, all factors must be taken into consideration in any given case The presence of one or two papules does not warrant a diagnosis, neither does dryness and desquamation The lesions are falsely exaggerated by cold (gooseflesh) Naturally the rash can be improved by a bath, a fact sometimes cited as evidence against its being the result of vitamin A deficiency The excess cornified epithelium is removed mechanically Finally, and unfortunately confusion has arisen because of the time lag in both the appearance and disappearance of the eruption in relation to blood levels of vitamin A dark adaptation tests and treatment with vitamin A

It must be remembered that considerable time is required for the structural changes in the skin to occur, both in the development of the lesion and in its restoration to normal while changes in the concentration of vitamin A in the blood (particularly an increase) and in dark adaptation can occur many times more rapidly Hence direct correlation with changes in the skin at any one time may fail

A few other lesions notably corns and calluses have been attributed to vitamin A deficiency [21] Though

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19 Mapson L. W and Walker S E The Synthesis of Ascorbic Acid in the Rat Deprived of Vitamin A With and Without Addition of Chloretone Brit. J Nutrition **2** 1 1948 *Jonsson G Obel A. L* and Sjoberg K Skorbut als Sekundarerscheinung bei A Avitaminose Ztschr f Vitaminforsch **12** 300 1942 Mayer J and Krehl W A Scorbutic Symptoms in Vitamin A Deficient Rats Arch Biochem **16**: 313 1948

20 Sure B Theis R M and *Harrelson* R T Vitamin Interrelationship 1 Influence of Avitaminosis A on Ascorbic Acid Content of Various Tissues and Endocrines J Biol Chem **129** 245 1939

21 Straumfjord, J V Lesions of Vitamin A Deficiency Their Local Character and Chronicity Northwest Med. **41** *229 1942*

such a relationship has not been established, a fairly good case theoretically, could be made for it Such lesions consist essentially of an increased local cornification, which might occur on the basis of a local, relative deficiency induced by pressure ischemia or some similar cause In relating any such possibility to treatment full consideration must be given to the long time needed to produce significant changes

Diagnosis—Recognition or detection of vitamin A deficiency rests on the diagnostic triad of history physical examination and laboratory tests The history includes inquiry not only into the symptoms but into the dietary (or other) intake of vitamin A The symptoms are usually conjunctivitis asthenopia dryness of the eyes, difficulty in vision (even night blindness) and the eruption In more advanced cases there are of course severe ocular symptoms Children fail to gain weight, which for them is probably the first symptom, and, if pulmonary complications develop, they exhibit the usual symptoms of such disease Examination reveals the gross changes in the eyes mucous membranes and skin previously described In advanced disease night blindness is detected by gross testing

There are three laboratory or special tests A test of dark adaptation examination of smears from epithelial surfaces for cornification of the epithelium and determination of the concentration of vitamin A and carotene in the blood

Tests of dark adaptation with suitable adaptometer or photometer will undoubtedly detect a mild or severer grade of night blindness due to vitamin A deficiency Vitamin A deficiency is not the only cause of night blindness but that need not destroy the value or significance of the test if it is employed properly The greater difficulty comes with extremely slight grades of night blindness or better still extremely slight variations in dark adaptation detected by means of an accurate photometer Such variations are frequently within the limits of error resulting from such factors as subjective response learning factor motivation and slight errors in technic It is not surprising therefore that failure to correlate variations in photometric measurements with other data such as dietary intake,

levels of vitamin A in the blood and history and physical signs should have occurred Also, regardless of diet and preceding stores of vitamin A, children who have colds and certain other minor ailments show poor adaptation promptly Adaptation returns to normal with recovery from the illness In selecting subjects with poor adaptation some investigators may have selected those who were temporarily affected with minor illness With recovery from the illness adaptation improved irrespective of vitamin A additions A learning factor is not involved in such circumstances This should not be taken as an excuse for the use of inaccurate or improper instruments but it does mean that standards should be adopted based on careful experimental evidence which will clearly differentiate real changes in dark adaptation Even with this limitation it is possible that night blindness can be detected by instrumental means earlier than otherwise and the proper instruments should be used for this purpose Other causes of night blindness must of course be eliminated before the condition can be attributed to vitamin A deficiency but ordinarily this is easy It should be remembered however that vitamin A deficiency can probably occur and manifest itself before night blindness develops although in man night blindness can occur and be demonstrated before corneal and conjunctival changes become grossly apparent In experimental animals the concentration of vitamin A in the retina may remain normal while that of the blood is reduced greatly and under treatment returns to normal before that of the blood [5] Finally other ocular defects, including those due to other nutritional deficiencies may cause error

Microscopic examination of scrapings from the nose to determine the presence of cornification of the epithelium has been recommended in the diagnosis of the condition in infants [2] Similar examination of scrapings from the scleras and corneas has been suggested for use with adults In my experience the latter is neither suitable nor reliable at least for the diagnosis of slight deficiency [3] In the same category is the

22 Sweet, L. K and K A g H J Clin cal and Anatomic Study of Av taminosis A Among the Chinese Am. J Dis Child. 50 699 (Sept.) 1935

3 Youmans J B Co lette, M B Corlette M G and Frank H Inadequacy of Conjunctival Sm ar n the Diagno is of Sl ght Vitamin A Deficiency in Adults J Lab & Clin Med. 25 665 1938

demonstration of excessive epithelium in urinary sediments or vaginal smears, although this should arouse suspicion of a possible vitamin A deficiency

Determination of the concentration of vitamin A and carotene in the blood is useful in diagnosis and is probably the best laboratory aid The concentrations of the two substances do not necessarily parallel each other however Carotene values are easily influenced by dietary intake, hepatic disease or disorders of absorption, without of necessity, the concentration of vitamin A being affected For this reason, the two determinations are useful in differential diagnosis of such other diseases as sprue and hepatitis For the diagnosis of vitamin A deficiency, the vitamin A concentration is much more helpful and reliable Low values are found in a fully developed deficiency However, the storage of vitamin A is ordinarily great in adults and a considerable time is needed to deplete these stores The exact levels at which vitamin A deficiency actually exists have not been established In part, this is due to dissimilarity of method and the failure of the various investigators to follow similar procedures In experimental animals the concentration of vitamin A in the blood has been observed to have fallen to 10 per cent or less of normal before microscopic lesions were detected in the eyes [5]

Several methods nearly all of which use the Carr Price reaction and involve the use of a photoelectric colorimeter are available [24] Those are probably the most practical for ordinary clinical use A micromethod, using the measurement of ultraviolet ray absorption with a spectrophotometer has been developed [25] and is useful when one is dealing with small amounts of blood or making mass determinations Recently other technics have been introduced which may offer certain advantages [26]

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24 Clausen S W and McCord A. B The Carotenoids and Vitamin A of the Blood *J Ped at* **13** *635 1938* *Kimble M S The Photo*colo metr c Determination of Vitam n A and Carotene n Human Plasma, J Lab & Clin Med **24** 1055 1939 May C D Blackfan K D McCreary J F and Allen F H Jr Cl n cal Stud s of Vitamin A n Infants and in Children Am J Dis Child **59** 1167 (Ju e) 1940 Dann W J and Evelyn K. A The Determ nation of Vit min A w th the Photoelect c Color meter B ochem J **32** 1008 1938 Josephs H W Studies in Vitamin A Rel tion of Vitamin A and Carotene to Serum L p ds Bull Johns Hopkins Hosp **65** 112 *1939*

25 Bessey O A Lowry O H Brock M J and L pez J A The Dete minat n of V tam n A and Carotene in Small Quant ties of Blood Serum J Biol Chem **166**: 177 1946

26 Sobel A E and Snow S D The Est mation of Serum Vitam n A with Activated Glyce ol Dichlorohydrin J B ol Chem. **171**: 617 1947

No final agreement has been reached on normal standards for vitamin A There is a wide acceptance of a lower normal value for adults of 70 international units (approximately 20 micrograms) per hundred milliliters of serum or plasma Values for infants may be lower, but an exact level cannot be stated with certainty Some evidence suggests 20 micrograms as the lower normal value for infants

Studies of experimental deprivation in humans [27] showed clearly that no symptoms or signs appeared until the concentration in the serum dropped below 40 international units (approximately 12 micrograms) per hundred milliliters The earliest manifestation was night blindness detected by instrumental methods

Accordingly it would appear that values below 40 international units per hundred milliliters of serum or plasma may be associated with clinical evidence of deficiency but must be interpreted in the light of other evidence The lowest value found by Lewis and his associates [28] in what they considered normal infants was 45 international units per hundred milliliters and this value has been suggested as a low normal level Values below this were associated with deficient diets and disorders of fat absorption Children 6 to 12 years old had concentrations similar to those of adults Conservatism would require that the concentration be extremely low before it is considered strong evidence of an actual deficiency, especially in the absence of other evidence

As indicated carotene values are so much affected by intake and other factors not necessarily related to a deficiency of vitamin A that they are of much less use in the diagnosis of this condition The usual figures in normal healthy adults appear to be between 60 and 200 micrograms per hundred milliliters Low values (below 30 micrograms in adults) are usually associated with either a low intake or defective intestinal absorption In infants, the serum or plasma carotene level is usually zero or approximately that until quantities of green and yellow vegetables and fruits or other carotene containing foods are eaten

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27 *Vitamin A Deficiency and the Requirements of Human Adults* Report of the Vitamin A Sub Committee of the Accessory Food Factors Committee Nature **156** 11 1945

28 Lewis J M Bodansky O and Haig C Level of Vitamin A in Blood as Index of Vitamin A Deficiency in Infants and in Children Am J Dis Child. **62**: 1129 (Dec) 1941

demonstration of excessive epithelium in urinary sediments or vaginal smears, although this should arouse suspicion of a possible vitamin A deficiency

Determination of the concentration of vitamin A and carotene in the blood is useful in diagnosis and is probably the best laboratory aid The concentrations of the two substances do not necessarily parallel each other, however Carotene values are easily influenced by dietary intake, hepatic disease or disorders of absorption, without, of necessity, the concentration of vitamin A being affected For this reason the two determinations are useful in differential diagnosis of such other diseases as sprue and hepatitis For the diagnosis of vitamin A deficiency, the vitamin A concentration is much more helpful and reliable Low values are found in a fully developed deficiency However, the storage of vitamin A is ordinarily great in adults, and a considerable time is needed to deplete these stores The exact levels at which vitamin A deficiency actually exists have not been established In part this is due to dissimilarity of method and the failure of the various investigators to follow similar procedures In experimental animals the concentration of vitamin A in the blood has been observed to have fallen to 10 per cent or less of normal before microscopic lesions were detected in the eyes [5]

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24 Clausen S W and McCord A B The Carotenoids and Vitamin A of the Blood J Pediat **13** 635 1938 Kimble M S The Photocolorimetric Determination of Vitamin A and Carotene in Human Plasma J Lab & Clin Med **24** 1055 1939 May C D Blackfan K D McCrary J F and Allen F H Jr Clinical Studies of Vitamin A in Infants and in Children Am J Dis Child **59** 1167 (June) 1940 Dann W J and Evelyn K A The Determination of Vitamin A with the Photoelectric Colorimeter Biochem J **32**: 1008 1938 Josephs H W Studies in Vitamin A Relation of Vitamin A and Carotene to Serum Lipids Bull Johns Hopkins Hosp **65**: 112 1939

25 Bessey O A Lowry O H Brock M J and Lopez J A The Determination of Vitamin A and Carotene in Small Quantities of Blood Serum J Biol Chem **166** 177 1946

26 Sobel A E and Snow S D The Estimation of Serum Vitamin A with Activated Glycerol Dichlorohydrin J Biol Chem. **171** 617 1947

In a survey of the blood levels of vitamin A in school children in New York State, Bessey and Lowry[31] found 0 to 1 per cent of those tested in eight different schools with values below 70 international units per hundred milliliters From 1 to 10 per cent had values below 105 international units which the authors classed as fair The incidence of the dermatosis in a group of soldiers during the war ranged from 4 to 26 per cent[32] The actual incidence is probably somewhat less than indicated by these observations but it must be remembered that a greater frequency is to be expected among such a selected group as persons ill with other diseases

Treatment—Except for scarring of such tissues as the eyes the lesions of vitamin A deficiency should respond to adequate treatment with the vitamin In accordance with general principles functional changes represented by the night blindness should respond promptly and structural changes such as the dermatosis more slowly the latter often only over a period of several weeks Except in unusual circumstances small to moderate doses—10 000 to 40 000 units daily —are all that are needed There is no evidence that structural lesions will respond more rapidly to excessively large doses unless there is difficulty of absorption. Two exceptions to this general principle probably exist in patients, especially infants or children, with acute keratomalacia and in infants with involvement of the bronchi atelectasis and pneumonia In such instances much larger doses 50 000 to 100,000 units may be used empirically with the hope of more quickly stopping the process before irreparable damage or death occurs There may be a paradoxic exacerbation of symptoms at the onset of treatment (due to a sudden sloughing of large masses of cornified epithelium) Occasionally massive doses 500 000 units or more, may be required to overcome difficulties of absorption or individual peculiarities

The preparations of choice are the fish liver oils or concentrates There are many forms containing up

31 Bessey O A., and Lowry O H. Nutritional Assay of 1,200 New York State School Children, *Report of the New York State Joint Legislative Committee on Nutrition*, 1947

32. Report on Project No. 30 Test of Acceptability and Adequacy of United States Army C, K, 10-in-1 and Canadian Army Mess Tin Rations, Armored Medical Research Laboratory Fort Knox, Ky., *Office of the Surgeon General of the Army* Washington, D C., 1944

Temporary fluctuations in the concentration of vitamin A occur as an effect of the ingestion of alcohol or fever, but ordinary meals do not affect the concentration and it is not necessary that the blood be tested with the patient in the fasting state A rise occurs after the administration of large doses of the vitamin, and a tolerance test may be used such as that proposed by Ruch, Brunsting and Osterberg [29] Such a test is also used in the diagnosis of other diseases, especially those affecting the absorption of fat

For the reasons stated correlation between blood levels and other aspects of vitamin A nutrition and deficiency need not occur and may not be observed when they are present unless due allowance is made for the time lag factor

Incidence—The incidence of actual vitamin A deficiency is unknown Xerophthalmia and keratomalacia are certainly rare in adults in this country They are not common in children The same may be said of frank night blindness What the incidence of mild deficiency—as represented by slight (detectable only with instruments) grades of night blindness slight dermatosis or debatable changes in the scleras may be—depends on one s interpretation and evaluation of such signs The strikingly high incidence based on adaptometer readings which was reported so frequently a few years ago seems scarcely credible. In a survey of a general population [30] only 11 of 450 subjects tested had values for serum vitamin A below 30 international units per hundred milliliters (0 to 29) Of these 8 were children (under 15 years of age), although these values are probably significant even for them Forty-five, or 18 per cent of the adults (21 years of age or over) had less than 70 units Of this latter group 33 per cent had greater or lesser impairment of dark adaptation as measured with an adaptometer (Hecht) In the total population of approximately 1 200 persons only some 35 or about 3 per cent had a dermatosis This dermatosis however was found in about one fifth of the 40 white male subjects of the age group 16 to 20

29 Ruch D M Brunsting L. A and Osterberg A E Use of Vitamin A Tolerance Test in Certain Cases of Dermatologic Disorders Proc Staff Meet. Mayo Clin 21 209 1946

30 Youmans J B Patton E. W Sutton W R. Kern R and Steinkamp R Surveys of the Nutrition of Populations (3) The Vitamin A Nutrition of a Rural Population in Middle Tennessee, Am. J Pub Health 34 368 1944

disease range in severity from slight, undetectable changes to those severe enough to be fatal The changes are primarily structural although disturbances in function directly dependent on structural abnormalities do occur It is important to remember that deformities, which are the scars' and residue of structural changes, may persist after the deficiency of vitamin D has been relieved and the rickets cured, leaving forever mute evidence of the illness Such deformities or scars should never be interpreted as indicating an existing deficiency of vitamin D

The earliest detectable change in rickets probably is the increase in alkaline phosphatase This is soon followed by a decrease in the blood phosphorus The second stage is the roentgenographic appearance of abnormalities in the skeleton detectable only roentgenographically The third is the development of physical changes observable on ordinary examination These range from slight to gross alterations in skeletal structure, with various accompanying signs and symptoms Other symptoms not related to the skeletal system, may be present

Because rachitis occurs in growing bone the most active lesions are to be found in the part of the bones growing most rapidly the junction of the epiphysis and diaphysis and corresponding areas in the flat bones The earliest changes in the bones are microscopic and consist of a disorderliness and disarrangement of the normal pattern which is one of great orderliness and regularity In the zone of proliferation the cartilage cells instead of degenerating evenly and uniformly just before the capillaries reach them fail to degenerate and be absorbed The region of the proliferating cartilage enlarges because the cells fail to die, and large masses pile up in irregular fashion The capillaries eventually reach and destroy them but the process is irregular The line of advance instead of being even is irregular Even where the capillaries do advance masses or islands of cartilage cells may persist Cells on the outside of the mass are abnormal in appearance and staining Some of the original matrix is destroyed but some remains calcified and uncalcified On this osteoblasts lay down osteoid tissue and build irregular chondro osteoid trabeculae Depending on the stage of the rickets this osteoid bone either completely fails to calcify or does so irregularly and incompletely

to 60,000 international units per hundred milliliters Care should be taken, when massive doses are used, to guard against overdosage with vitamin D, which is present in relatively high concentration in some preparations Large doses may cause nausea and anorexia Recently, parenteral preparations have become available, but they are rarely needed Aside from the specific treatment, little is needed but ordinary cleanliness

VITAMIN D

Rickets is the result of a deficiency of vitamin D and it is interesting to note that all stages of the deficiency, from mild to severe are thought of and written of as rickets and not as has been the case with some other vitamins, called rickets only when clearly manifest and given some other name when less severe Rickets is a disease of growing bone and hence does not occur in adults Vitamin D deficiency in adults is perhaps best called osteomalacia

Confusion has sometimes arisen because other factors may affect the occurrence of rickets, particularly experimentally and in animals For example grossly abnormal diets favor the development of rickets (actually cause it in some animals) other deficiencies notably that of calcium, may complicate rickets, with a resulting tetany and a clinical picture resembling rickets but unrelated to a deficiency of vitamin D can occur Rickets may also occur in premature infants as a result of calcium and phosphorus deficiency when human milk is fed and not supplemented A deficiency of vitamin D is, however, the common and primary cause of rickets

The nature of the group of substances included under the name vitamin D together with relationships and action, has been described elsewhere [33] Whether other effects are attributable to a deficiency of these substances and whether they are concerned with some of the nonosseous manifestations of rickets is unknown

The clinical manifestations of rickets are too well *known to warrant extensive description here* They involve the skeleton primarily [34] and, as in all deficiency

33 Handbook on Nutr tion chap 10 To be publ shed

34 Follis R H Jr The Pathol gy of Nutr tional Dis ase—Phys ological and Mo pholog cal Changes Wh ch Result from Deficiencies of the *Essential Elements Amino A ds V tamins* and F tty Acids Spring field Ill. Charles C Thomas Publ sher p 291 1948

ity The degree of restoration may be surprisingly great and may occur over months or years

Defects in tooth structure can be assumed to occur in rickets, although they may not be apparent and when present may be difficult to distinguish from the injury caused by lack of vitamins A or C Defects are most frequent in permanent teeth because rickets usually occurs at the time they are calcifying but defects can occur in the temporary teeth

Other pathologic changes consist of slight hypertrophy of the parathyroids and perhaps some atrophy of the thyroid cells The fibrosis and atrophy of muscles sometimes observed is probably not specific for rickets

The changes in nongrowing bone which may be the result of vitamin D deficiency, are described in the section on calcium deficiency and osteomalacia Albright and his associates have reviewed and summarized their studies of this condition and have presented a critical review of the literature [35] According to them vitamin D deficiency and the osteomalacia accompanying it is of three kinds (1) that due to simple lack of vitamin D, (2) that due to vitamin D resistance and (3) that due to vitamin D deficiency accompanying steatorrhea There is little doubt that as these authors indicate simple lack of vitamin D in adults is uncommon in this country That due to steatorrhea is of course a conditioned deficiency occurring under a variety of conditions causing the steatorrhea The vitamin D resistant group is similar to the group with 'resistant rickets already mentioned However in one case recently reported by McCance [36] the resistance (and deficiency) apparently did not develop until the patient was 15 years old McCance states that other similar cases have been reported The patient reported by McCance showed pseudofractures on roentgen examination similar to those described by Milkman [37] and known as Milkman s syndrome

35 Albright, F Burnett C H Parson W Reifenstein E C Jr and Roos A Osteomalacia and Late Rickets The Various Etiologies Met in the United States with Emphasis on That Resulting from a Specific Form of Renal Acidosis the Therapeutic Indications for Each Etiological Sub-Group and the Relationship Between Osteomalacia and Milkman s Syndrome, Medicine 25 399 1946

36 McCance R A Osteomalacia with Looser s Nodes (Milkman s Syndrome) Due to a Raised Resistance to Vitamin D Acquired About the Age of 15 Years, Quart. J Med 16 3 1947

37 Milkman L. A Multiple Spontaneous Idiopathic Symmetrical Fractures Am. J Roentgenol. 32 6 1934

Into this rachitic intermediate zone extrusions and enlargements of the cartilage canals penetrate from the distal side in the more severe cases and sometimes from the shaft and side (perichondrial) as well The amount of connective tissue brought in by blood vessels may be greatly increased

It is this rachitic intermediate zone which is responsible in large measure for the deformities It causes enlargement of the ends of the long bones as they increase in length and pushes the centers of ossification of the epiphysis further from the shaft Being osteoid *(soft) bone it is easily bent by the forces of posture* weight bearing and muscle pull The direction of the line of new growth is thus changed, and growth continues to follow the new direction even when it is at a considerable angle to the line of the shaft previously *formed Greater in size the intermediate zone becomes* too large for the shaft, spreads it and deflects the trabeculae outward Increased thickness of the shaft develops from increased perichondrial deposit of osteoid tissue Improper calcification and increased decalcification of the shaft softens the latter which *bends in* various directions Bending of the shaft is usually one of the later deformities

Changes similar to those described at the epiphysial diaphysial junction of growing long bones occur in all bone in the process of formation the osteoid *bone* being deficient in calcium salts Such changes can be seen in the cancellous portions of long bones in the cortex along the lacunas in the tables of the skull and elsewhere in the skeleton

Repair begins when vitamin D deficiency ceases and it begins in the area where normal ossification would *be occurring* had *not rickets intervened* leaving the abnormal area behind to be straightened out later The area where normal ossification begins appears as a dense white transverse line of healing on roentgenograms Next focal areas of healing appear and spread *gradually the capillaries and columns of car*tilage cells assume their regular form and the normal process of decalcification ossification and recalcification takes over Because there has been an abnormal excessive overgrowth of osteoid tissue there is a gradual selective *absorption which reduces the size of the mass,* straightens it out rearranges it and reduces the deform

evidence of activity or may shift between these various states If the rickets continues in a moderate or severe form during the first and second years the signs persist or increase, except for the craniotabes If the onset occurs then the changes are apt to be pronounced because of the effect of such forces as those induced by various postures Often the child is too weak to stand and to walk In such cases the deformities of the head are greater chest deformities increase, the spine becomes bowed (kyphosis) and the more severe deformities of the extremities such as bow legs appear Dentition is delayed and defective teeth are evident Roentgenograms may show one or more greenstick fractures of the long bones The anterior fontanelle may remain open at 2 years of age or older Weak children raised to a sitting posture assume a characteristic posture with the legs crossed and the hands supporting them at their sides Standing and walking increase the deformities of the legs and pelvis

Deformities are a product of the severity of the deficiency the developmental stage of the parts affected, the rate of growth and the physical stress to which the parts are subjected Reciprocally the more rapid the growth the more severe the rickets (because of the increase in the requirements of vitamin D)

Craniotabes which is not specific for rickets is essentially due to lack of calcification and consists of a softening and thinning of an area of the skull which indents and rebounds often with a crackle Similar changes occur in osteogenesis imperfecta in hydrocephalus and even in some normal (especially premature) infants The areas are spotty and nearly always posterior in rickets with ill defined edges varying in size from small (2 cm) to extremely large They are not usually bilateral They usually occur at 3 or 4 months of age In osteogenesis imperfecta the areas are larger and more widely distributed Those in normal infants usually are unilateral occur along suture lines and disappear before rickets appears Craniotabes is called the most reliable single bedside sign of rickets

Bosses on the skull occur on the surface because the bone there is mainly of periosteal origin Although the head is enlarged the cranial cavity is not increased

The commonest chest deformity the 'rachitic rosary ' may be difficult to detect in mild cases because the enlargement may be mainly on the inner surface If

Albright and his co-workers consider this syndrome a simple manifestation of osteomalacia and not a specific disease entity

In general, the symptoms of rickets are mild and rather vague Analysis of the food intake is of little value, except in relation to the use of supplements milk fortified with vitamin D, cod liver oil and similar substances *The need for these substances is so great* ordinarily that lack of them warrants a tentative diagnosis The physical signs of the disease are the deformities and abnormalities of the skeleton Usually the latter are the first things noted Craniotabes, which occurs at about 3 months of age, is usually the first to be found affecting a few small areas on the back of the head The cranial sutures are widened and the edges soft Later the 'rachitic rosary ' enlargement of the costochondral junctions and the wrists distal ulna and radius are observed Craniotabes may not occur if the disease begins later Constitutional symptoms are lacking in mild or moderately severe cases *and the infant may appear well, though rather pudgy* and pasty With severer rickets there are restlessness head sweating irritability and weakness, though it has been questioned whether some of these are truly a part of rickets Generally the severer the deficiency the earlier symptoms and signs appear

During the middle part of the first year unless deficiency is relieved the craniotabes is more widespread and weakness is greater Cranial deformities from pressure appear on the back and side of the head When the patient is 8 or 9 months of age the craniotabes disappears but the cranial deformities increase and frontal and parietal bosses cause the square head' and olympian brow The fontanelles remain open the frontal widely Additional deformities of the chest appear Harrison s groove depression of the sternum, chicken breast and lateral trough The enlargement of the ends of the ulna and radius as well as of the other long bones increases but may be masked by fat The child is less active and may have a pot belly'

It is evident that the progress of the disease and the development of deformities depend greatly on the supply of vitamin D intentional or fortuitous Thus the disease may progress rapidly and in severe degree may be held at relatively static levels of moderate severity may be nearly completely relieved with almost no

With the roentgenograms, one can examine the lesions at short intervals, observing the effect of treatment Because of accessibility and convenience, as well as early occurrence of changes, the lower radius and ulna are the usual sites for the clinical roentgen examination The principal changes are cupping spreading spur formation fringing stippling and changes in the shaft None are specific, and all are subject to interpretation Cupping is a concavity at the end of the shaft and is not consistent Spreading, referred to in the discussion of the pathology, is a widening of the end of the shaft and may or may not be accompanied by cupping It occurs in scurvy also. Spurs are calcified lines extending from the cortex of the shaft down along the side of the proliferating cartilage The alinement is often poor Spurs occur in congenital syphilis and to a slight extent in normal bones at times Fraying and fringing refer to narrow irregular tangled lines running from the shaft into the cartilage In the early stages they are thin and short in more severe cases thicker and longer They are reliable but not particularly early signs They occur in syphilis also Stippling gives an irregular dotted appearance to the end of the shaft It may appear early, but is also present late in the disease

Eliot and Park s[38] early in contrast to 'very early, signs consist of a lack of sharp definition of the edge of the distal end of the ulna away from the radius and a decreased density of the cortex in the same area This should not be confused with the normal irregularities associated with muscle attachment there Similar changes are found in the middle of the shaft of the radius and the proximal end of the ulna on the radial side as early evidence of periosteal proliferation and decreased cortical density Atrophic' changes are late but characteristic They consist of decreased density with irregular trabecular markings thin cortex and hair like shadows extending out from the shaft The cortex may be thickened on one side and the marrow cavity narrowed There may also be such severe changes as fractures distortions and displacements

The roentgenogram discloses changes induced by treatment (healing) which is also of diagnostic value

38 Eliot, M M and Park, E A Brennemann s Practice of Pediatrics by Various Authors edited by Irvine McQuarrie Hagerstown, Md. W F Prior Company Inc. 1948 vol. 1 chap 36

the rickets is at all severe, healing may leave permanent deformities In most cases respiratory obstruction is needed, besides rickets, to produce a pigeon breast Kyphosis develops with the sitting posture lordosis with standing and walking Lack of muscle tone is a factor The worst deformities of the pelvis occur when the rickets is prolonged into childhood, especially if the child can stand and walk despite the rickets These deformities are most familiar and important to the obstetrician as deformities in the childbearing woman

Deformities of the extremities usually occur rather late and are associated with sitting, standing and walking A variety of deformities may be present, *there is* both lateral and anterior bowing (saber shin bowleg and knock knee) As growth occurs the deformities shift their position, the forward bend of saber shin ascending from its location just above the ankle in infancy to the junction of the lower and middle third of the tibia In contrast to the saber shin of congenital syphilis in which the thickening is anterior the rachitic thickening is irregular and more posterior than anterior Coxa vara or a more acute angle of the neck of the femur on the shaft can cause a waddling gait

Nystagmus and head rolling and shaking may appear in addition to head sweating irritability and restlessness *The nystagmus may occur in any plane* and in either or both eyes and if bilateral is convergent Its exact relation to the rickets is unknown

Diagnosis —The most practical early diagnosis probably is made by roentgenogram However this is neither easy nor certain in the earliest stages and differences of opinion in respect to the interpretation of the roentgen findings may be encountered in any particular case Nevertheless long before any physical signs become *clearly* manifest *the* roentgen *changes are* definite and the changes in the alkaline phosphatase and phosphorus levels in the serum are available for supportive evidence for a diagnosis which should be suggested to the alert physician by the history of the infant Difficulty and error may occur in routine examination of apparently well infants if the disease is in its early stages In the more advanced stages of the deficiency the usual symptoms and physical changes *should be adequate for the establishment of the diagnosis* Such patients should reach the physician only when they have not previously had medical care

plete recovery, and hence the determination does not accurately reflect the actual progress or adequacy of treatment It is of little value in vitamin D deficiency in adults and in the intermediate period of childhood and adolescence it is difficult to tell in a given case whether the values are abnormal The generally accepted normal value for infants is 5 to 7 mg per hundred milliliters with few well infants below 5 mg and with 4 mg the beginning level for rickets, in which values may be even lower than 2 mg In adults the normal range is from 3 to 4 5 mg, and children and adolescents have values between those of infants and adults Determination of the concentration is of little or no value in adults

The concentration of calcium in the blood is often determined in suspected rickets and vitamin D deficiency In rachitic children and infants the values are usually normal (9 to 11 mg per hundred milliliters), though they may be reduced When these values are low the rickets may be complicated by tetany, but this is unusual The normal values are the same in adults and a lowered concentration of calcium in the blood caused by vitamin D deficiency, even with a low intake, is uncommon

The therapeutic test is of great value in rickets particularly when the effects of treatment are checked with repeated roentgen and blood examinations In adults with osteomalacia the relief of symptoms pain in particular is helpful

Incidence —The actual incidence of rickets is difficult to determine The general belief is that with modern knowledge of means of prevention on the part of physicians and the public and with the availability and widespread use of effective preparations of vitamin D the disease is now infrequent in this country There is evidence however that this belief is overly optimistic particularly in older children Follis Jackson and Park[40] on the basis of microscopic examination of autopsy material have reported an incidence of as high as 48 per cent in infants aged 3 to 19 months and 46 per cent in children up to 12 years of age In

40 Follis R H Jr Jackson D and Park E A The Problem of the Association of Rickets and Scurvy Am. J Dis Child. 60: 745 (Sept) 1940 Follis R H Jr Jackson D Eliot, M M and Park E A Prevalence of Rickets in Children Between 2 and 14 Years of Age ibid. 66: 1 1943

because it checks the therapeutic trial Recovery is marked by the deposit of lime salts and is seen at the junction of cartilage and shaft as a thin transparent line, faint and incomplete at first and later broad and heavy, even double It appears in the region where calcification would be occurring had not rickets developed and hence is in the distal portion of the intermediate zone at a considerable distance from the end of the shaft, the distance depending on the duration and severity of the disease As the osteoid trabeculae become calcified, the intermediate zone shows spotty shadows, and calcification appears in the periosteal encasements Alternate periods of remission and relapse due to treatment or natural variations cause various combinations of activity and healing

Measurement of the concentration of alkaline phosphatase in the blood, which rises in rickets is useful in diagnosis and may give evidence before changes in the roentgenogram can be detected thus being helpful in the diagnosis of early rickets Also, the concentration remains elevated long after treatment and healing are begun returning to normal only after the latter is complete or nearly complete Thus, it is a better measure of adequate treatment than the roentgenogram and has prognostic value The concentration is usually expressed in Bodansky units in this country Normal values for infants are 3 to 12 units No generally accepted standards are available for older children or adults, in whom the significance of variations is not well established A survey of a large general population gave values for adults[39] from 1 5 to 5 0 Bodansky units with a mean of approximately 3 0 units *Variations in serum phosphatase values may occur in conditions other than rickets or vitamin D deficiency, but this is of little practical importance in relation to its use in the diagnosis of rickets in infants It is a greater problem in older children and adults*

The determination of inorganic phosphorus in the serum is a useful clinical test for rickets but has certain drawbacks In early or slight rickets the values fall in the doubtful range Treatment causes a prompt rise to normal despite persisting disease and incom-

39 Youmans J B Patton E W Sutton W R Kern R and Steinkamp R Survey of the Nutr tion of P pulations (4) The V tam n D and Calcium Nutr tion of a Rural Population in M ddle Tenne s e Am J Pub Health 34 1049 1944

vitamin D This procedure has certain advantages, among them being the greater assurance that the vitamin is actually taken and the protection really given For these purposes a dose of 75 mg of calciferol (vitamin D_2) with an activity of 300,000 international units given in 1 ml of peanut oil after a milk feeding has been recommended[41] However, there is a possibility of at least mild toxicity with such a procedure

Ordinarily after the growth period the requirements will be met adequately by the usual exposure to sunlight and the preformed vitamin D consumed in the food Milk fortified with vitamin D contributes to these sources but should not be depended on for protection during the more susceptible period of infancy unless intake provides at least 400 units per day For supplements concentrated preparations of vitamin D—cod liver oil, fortified fish liver oil (halibut), concentrated fish liver oils (percomorph) or viosterol in oil—are needed The fish liver oils contain vitamin A which I believe is a decided advantage Fish liver oils contain vitamin D of animal nature Viosterol in oil has the advantage and disadvantage of small volume The concentration is adjusted to provide 222 units per drop, which permits the giving of large doses in a form not unpleasant to take and easy to administer The small amount can easily be lost however in containers Vitamin D in propylene glycol or alcohol provides a preparation miscible with water and hence easily incorporated in the infant s formula All preparations should be prescribed and administered in adequate dosage based on the concentration of the product in terms of international units Physicians should know the strength of the preparations they employ and should *prescribe on a unit basis*

Protection should be afforded to pregnant women, especially during the latter half of pregnancy and to *nursing mothers Both mother and child will be benefited* Moderate doses of 400 to 800 units a day will be sufficient except in unusual cases[42] Similar amounts will suffice for invalids and others kept indoors Spe-

41 Krestin D Treatment of Rickets with Single Massive Doses of Vitamin D_2 Lancet 1 81 1945

42 Dieckmann W J Diet from the Viewpoint of the Obstetrician, Nutrition Rev 6 1 9 1948

infants the use of the roentgenogram and other of the finer means of diagnosis indicates that minimal forms are more frequent than is commonly thought

It should be realized that the incidence is greatly affected by the environment Variations in ultraviolet radiation dependent on season latitude, smoke and housing affect the requirements of dietary vitamin D The incidence of rickets is greater in crowded, smoky cities among infants born so that their most susceptible period (4 to 6 months) comes during winter and in dark-skinned races Also, the more the confinement indoors the greater the incidence

It must be remembered, however, that in pointing out the probably rather large frequency of rickets, I am referring mainly to mild or minimal forms of the disease The incidence of florid severe rickets has undoubtedly been greatly reduced It must also be remembered that some at least of present day rickets is the result of greatly improved general health and care of infants leading to more rapid growth and hence to greater requirements of vitamin D than have been generally appreciated Some idea of the incidence of rickets in a rural area is furnished by the results of a survey [39] of some 94 subjects under 3 years of age which indicated an incidence of around 24 per cent Even this observation is made less significant however by one's inability in certain cases to distinguish between active and inactive rickets and the lack of close correspondence between the several criteria used in diagnosis It does however suggest the total rickets experience in the group

Congenital rickets is rare but it does occur and is apt to be severe in premature infants and twins

Treatment—Rickets should be prevented rather than treated but there are always some children who escape preventive measures in one manner or another and require treatment Standard preventive measures for the usual infant involve the administration of 200 international units of vitamin D from birth This dose should be increased in a few days to 400 units All infants should be protected during the first two years of life and in the light of present knowledge it would be well if some degree of protection were used during the growing period Protection for an entire season can be afforded by the administration of a single large dose of

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41 Krestin D T eatment of R ckets with Single Massive Doses of Vitam n D_2, Lancet 1:781 1945

42 Dieckmann W J Diet from the Viewpoint of the Ob tetrician, Nutrition Rev 6 129 1948

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early and partial healing effect of the vitamin This effect is more likely to occur in the severer cases of rickets and, if anticipated, can be prevented by the administration of calcium Calcium will also relieve tetany Calcium can be given as the chloride lactate or gluconate but the chloride is somewhat more effective in these circumstances An initial dose of 3 to 4 Gm followed by 1 Gm three or four times daily with the dose gradually decreasing after three or four days, is usually adequate

In adults, vitamin D deficiency is usually mild and easily relieved by ordinary doses of vitamin D It is usually helpful if some calcium is given in addition to the vitamin, since many cases in adults represent a dual deficiency Doses of 1,200 to 1 600 units per day will ordinarily suffice Failure of the vitamin to relieve the condition (a common experience) indicates that the simple deficiency of vitamin D with or without calcium deficiency is not the cause and that some other disease, such as hyperparathyroidism is present

Hypervitaminosis D—Poisoning from vitamin D in the prevention and cure of rickets is uncommon although doses of 1 500 units continued over a period of months may be mildly toxic Patients with so called resistant rickets tolerate the larger doses needed without harm However vitamin D is sometimes used in tremendously large doses in the treatment of a variety of diseases For these purposes doses as large as 1 000 000 units or more daily have been advised In these circumstances poisoning can occur Early symptoms are anorexia nausea headaches diarrhea and, in children pallor and lassitude There is an increase in the calcium content of the blood although there need be no direct relation of symptoms to the blood calcium Calcium crystals and casts may be found in the urine, and metastatic calcification may occur

VITAMIN K

Vitamin K is rather abundant in food and is formed in the intestine by the action of bacteria therefore deficiencies of the vitamin are rarely the result of a dietary inadequacy Rather, a deficiency occurs because of some condition which interferes with the production of the vitamin in the intestine or its absorption from the gastrointestinal tract In the latter cate

cial attention to the intake of calcium and phosphorus must be given to twins and premature infants

Much more active treatment is required for the cure of rickets Daily doses of 1,200 units will be sufficient in ordinary cases Much larger doses 5,000 to 10 000 units per day, will sometimes be required When extremely large doses are used, the concentrated prep arations are a practical necessity About three weeks are required to determine the effectiveness of a given dose and one should not hesitate to increase the dose drastically if improvement does not occur or is unsat isfactory The concentration of inorganic phosphorus in the serum should begin to increase in about ten days and roentgenographic evidence of healing should appear in about three weeks but the mere presence of these changes does not mean that the cure is complete The phosphatase concentration will remain elevated until a cure is obtained Deformities are corrected slowly and old deformities (scars) should not be interpreted as evidence of active rickets

As the disease is controlled, the dose can be reduced, but amounts larger than the usual protective doses should be continued for several months The aim in the treatment of rickets is to stop the progress of the disease as soon as possible and bring about a cure before deformities can develop or increase For this reason large doses may even be lifesaving in occasional cases of severe rickets in which the weakness of the ribs may cause danger of asphyxiation

Occasionally cases of so called refractory rickets are seen These are usually found in children 3 years of age and over who seem to have some individual peculiarity with respect to vitamin D Most of these will respond to extremely large doses 50 000 to 100 000 units In rare cases 1 000 000 to 1,500 000 units may be needed to secure an effect [35] High maintenance doses are also necessary Refractoriness suggests an incorrect diagnosis and especially the presence of one of the rickets like diseases caused by metabolic disturbances

In rickets complicated by tetany sufficient calcium may be supplied with the milk provided the intake is adequate Treatment of rickets with vitamin D may precipitate tetany by the sudden withdrawal of calcium from the blood to deposit in the skeleton under the

since vitamin K production in the intestine brings it to a close if death does not occur earlier This results from the fact that the principal source of vitamin K in infants is its production by bacteria in the intestine[43] and that the intestine of the newborn child is sterile and some days are required for the development of an intestinal flora, since only a small amount may be given the infant by its mother The disease is also rather clearly defined in point of onset and duration rarely beginning before the second or third day of life, with recovery by the seventh or eighth Death rarely occurs after the third day There is usually bleeding at multiple sites, such as skin, external mucosal surfaces hollow viscera, brain and lungs with the mucous membranes being especially affected Death results from debility and loss of blood Accompanying the hemorrhage, which is usually oozing in nature but persistent there may be fever and diarrhea

The relation of this deficiency and the hemorrhagic state to birth trauma, cerebral birth injuries and resulting spastic paraplegia and related disorders is not clear It has been suggested that, although some hemorrhage might well result from birth trauma it usually would not except in cases in which there might be a diminished prothrombin level be sufficient to cause significant injury However vitamin K deficiency and diminished amounts of prothrombin might exaggerate and prolong the initial hemorrhage into excessive bleeding Certainly other hemorrhages occur in these circumstances and are clearly visible but they lack the potential seriousness of the cerebral (meningeal) bleeding

Clinically the greatest amount of vitamin K deficiency is probably that associated with and resulting from jaundiced states the deficiency resulting from the interference with the absorption of fat and, hence of vitamin K from the intestine A second considerable number of cases are those in which the deficiency accompanies various diseases of the intestines with disorders of absorption including sprue In persons with diseases amenable to surgical intervention the bleeding is most important in relation to operative procedures to which it constituted a threatening and dangerous complication in the days before vitamin K In other cases it is

43 Kornberg A Daft F S and Sebrell W H Mechanism of Production of Vitamin K Deficiency in Rats by Sulfonamides J Biol Chem 155 193 1944

gory are included various gastrointestinal disorders such as ulcerative enteritis Also because it is a fat soluble vitamin, the various conditions interfering with the absorption of fat such as obstructive jaundice, sprue and celiac disease may interfere with the production of vitamin K As far as is known, its sole function in man is its participation in the formation of prothrombin Prothrombin is one of the substances involved in the clotting of blood When there is a deficiency of prothrombin there is delay in or failure of clotting with the result that hemorrhage may occur A deficiency of vitamin K by lessening prothrombin formation, delays clotting and is manifested by hemorrhage It is believed that prothrombin is formed in the liver, but the exact part which vitamin K plays in its production is unknown It is to be remembered however that other factors such as the function of the liver itself are concerned and in some cases of liver damage prothrombin formation may be deficient although even excess quantities of vitamin K are available

The abnormality resulting from vitamin K deficiency itself can be considered entirely functional and the organic changes simply those of the resulting hemorrhage These changes do not differ from those of hemorrhage of other origin It should be remembered however that the hemorrhage in vitamin K deficiency is not spontaneous it follows trauma even though that trauma may be relatively slight The defect is in the clotting after bleeding has begun Vitamin K deficiency does not precipitate bleeding

The clinical picture of the deficiency therefore is that of hemorrhage divided into three main groups (1) hemorrhage of the newborn (2) hemorrhage associated with disorders of intestinal absorption particularly those resulting from obstructive jaundice or interference with the production of vitamin K by the bacteria in the intestine as might be the case after prolonged use of such drugs as the sulfonamides and (3) a simple form of hemorrhage accompanying general malnutrition and inadequate intake of food The last is as previously stated uncommon the bleeding being present in the simple form of subcutaneous hemorrhages petechiae and purpura

In the newborn the disease is striking and clear cut As might be expected it is practically self-limited

rates in recent years of both mature and premature infants is partly attributable to the routine use of vitamin K

Treatment—A number of "artificial" vitamin K's, more potent than the natural form, have been developed One of these, 2 methyl 1, 4 naphthoquinone, is the preparation commonly used in treatment under the name menadione U S P A water soluble form menadione sodium bisulfite U S P, does not require the concomitant use of bile salts when given by mouth to jaundiced patients The water-soluble form contains not less than 49 per cent menadione Preparations of both forms of menadione are available for injection

Vitamin K is somewhat more effective and faster in action when given by mouth than by parenteral injection, but there are some advantages to the latter route in some cases Vitamin K is often given prophylactically, particularly to patients with diseases which may lead to vitamin K deficiency and to the newborn For the latter purpose the prophylaxis is usually accomplished by treating the mother for a short period before delivery For this purpose the equivalent of 1 mg of synthetic vitamin K (menadione) is given daily for several days just prior to delivery or once weekly during the last few weeks of pregnancy and at the onset of labor The advisability of routine treatment of the mother to prevent hemorrhagic disease of the newborn is still debated According to Eastman[46] vitamin K should be given to all women as soon as labor starts

If the infant is treated directly the equivalent of 0 5 mg is given at birth and 1 0 mg daily is given in divided doses for two or three days thereafter It may be placed on the back of the infant s tongue or added to the feeding or water Protection is particularly necessary for infants under a week of age who are to undergo surgical procedures

Other patients can be protected in the same way and with approximately the same doses The effect of treatment can be checked and a guide to dosage obtained by a repetition of the prothrombin concentration tests If the vitamin cannot be taken by mouth it can be given by duodenal tube or by parenteral injection Doses larger than 5 mg are rarely needed

If a deficiency already exists prompt treatment is important especially in the newborn Prophylactic doses will usually suffice for treatment of newborn

familiar as the symptomatic purpura of malnutrition, although even more extensive bleeding can occur in these circumstances

Diagnosis—Vitamin K deficiency is detected by the appearance of hemorrhage and by a determination of the concentration of prothrombin in the blood For practical purposes, the deficiency is confirmed by the increase in prothrombin following treatment with vitamin K The deficiency should be suspected from a knowledge of the patient, and confirmed by the prothrombin test and the hemorrhage should be prevented if possible Fairly simple and reliable tests for the concentration of prothrombin exist and can be repeated readily Of these those of Quick and Grossman [44] and Ziffern, Owen Hoffman and Smith [45] are the most useful and satisfactory clinically Vitamin K deficiency is one of the few deficiencies in which a quantitative measurement of the body's vitamin store or reserve is possible permitting an accurate determination of the point at which a true deficiency occurs At a prothrombin level below 20 per cent of normal a delay in clotting appears The test should be made in all cases of suspected deficiency The tests are not specific however and should always be checked by the administration of a few doses of a suitable vitamin K preparation

Incidence—The incidence of vitamin K deficiency in the general population is unknown Most studies have included only special groups such as the newborn and pregnant women The deficiency is known to occur frequently in patients with sprue jaundice and other diseases which interfere with intestinal absorption especially fat absorption It is also found in malnutrition It is apparent therefore that except for the newborn the disease will most often be found among patients ill with other disease

The incidence among the newborn is uncertain and differences of opinion concerning it exist among obstetricians Eastman [46] believes that among his patients at least hemorrhagic disease of the newborn is relatively common and that the dramatic decrease in mortality

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44 Quick, A J and G ossman A M Nature of Hemorrhagic Dase of Newborn Delayed Restorat on of Prothromb n Level Am J M Sc **199** 1 1940

45 Ziffern S E Owen C A Hoffman G R and Smith H P Control of Vitam n K Th rapy Comp to y Mechan sm at Low Prothromb n Level Proc Soc Exper Biol & Med **40** 595 1939 McGrath T B T chn que of the Proth omb n T me Dete mination Am J Clin Path (suppl) **3** 187 1939

46 Eastman N J Prematurity from the Viewpo nt of the Obstetrician Am. Pract **1**: 343 1947

CHAPTER XXII

DEFICIENCIES OF THE WATER SOLUBLE VITAMINS

JOHN B YOUMANS

THIAMINE

There is probably no other vitamin, with the possible exception of vitamin C for which the need in man is more clearly demonstrated than thiamine, no other vitamin for which, with the exception of some question about intestinal formation dependence on outside sources is so clearly demonstrated, no other vitamin about which so much is known of the intimate biochemical reactions in which it participates without knowledge of the mechanism by which a deficiency causes the symptoms, physical signs and functional and organic lesions that accompany that deficiency

The chemical nature biochemistry and physiology of thiamine have been described in detail elsewhere, as has the chemical lesion of the deficiency[1] The effects of a deficiency are peripheral neuritis and congestive heart failure In addition to these clearcut unmistakable functional and structural disorders, there are, apparently, disturbances in the psyche[2] and possibly in certain endocrine functions[3]

Pathologic Changes—The mechanism by which the chemical lesions of thiamine deficiency produce the structural changes in the peripheral nerves is unknown The lesion consists of a panneuritis, beginning with

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1 Handbook of Nutrition to be published

2 (a) Williams R. D Mason H L. Power M H and Wilder R M Induced Thiamine (Vitamin B_1) Deficiency in Man Relation of Depletion of Thiamine to Development of Biochemical Defect and of Polyneuropathy Arch Int. Med **71**:38 *1943* *(b) Hulse M C* and others Subclinical Vitamin Deficiency Assay of Subclinical Thiamine Deficiency Ann Int Med **21**:440 1944

3 (a) Musselman M M Nutritional Diseases in Cabanatuan War Med **8** 325 1945 Biskind M S Nutritional Deficiency in the *Etiology* of Menorrhagia Metrorrhagia, Cystic Mastitis and Premenstrual Tension Treatment With Vitamin B Complex, J Clin. Endocrinol. **3** 227 1943 (*b*) Klatskin G Salter W T and *Humm, F D Gynecomastia* Due to Malnutrition I Clinical Studie Am. J M Sc **213**:19 1947 (*c*) Gynecomastia Due to Malnutrition II Endocrine Studies, Am. J M Sc. **213**:31 1947

infants These prophylactic doses should be increased if the response does not appear or is delayed Progress should be checked with the prothrombin test Post operatively, caution must be taken that loss of blood and subsequent dilution with fluids does not reduce previously adequate vitamin K levels to pathologic levels In some patients treatment must be continued at intervals

In treatment of prothrombin deficiency resulting from the administration of dicumarol,[*] 64 mg of menadione sodium bisulfite administered intravenously has been found effective in some cases, though the response is sometimes undesirably slow This dose is equivalent to 40 mg of menadione Occasionally this condition does not respond to these large doses of vitamin K when it does not whole blood should be administered

VITAMIN E

It is still customary to include vitamin E among those vitamins for which a relationship to deficiency and disease in man has been demonstrated The correctness of this may be doubted seriously and there seems little justification at present for the inclusion of a description of the supposed symptomatology and pathology of vitamin E deficiency in a discussion of the vitamin deficiency diseases of man There is nothing in the well known signs symptoms and pathologic changes of repeated and threatened abortion to indicate that they bear any specific relation to a deficiency of the tocopherols except in some extremely dubious responses dubious in the clinical as well as statistical sense to treatment with the vitamin None of the other pathologic changes noted in animals—testicular degeneration degenerative changes in the muscles pigmentation of the uterus and the muscular layers of the seminal vesicles degeneration of the convoluted tubules of the kidney and changes in hair skin and various endocrine glands—have been shown to have their counterpart in man Neither have reports of specific effects of the vitamin in such diseases as muscular dystrophy in man been corroborated All this is the more important because vitamin E and a number of closely related substances are well known identified isolated and synthesized substances a situation which usually is helpful in establishing function and relationship to disease This does not mean however, that a relationship of vitamin E to requirements and disease in man will not be established simply that so far it has not been done

CHAPTER XXII

DEFICIENCIES OF THE WATER-SOLUBLE VITAMINS

JOHN B YOUMANS

THIAMINE

There is probably no other vitamin with the possible exception of vitamin C for which the need in man is more clearly demonstrated than thiamine, no other vitamin for which with the exception of some question about intestinal formation dependence on outside sources is so clearly demonstrated no other vitamin about which so much is known of the intimate biochemical reactions in which it participates without knowledge of the mechanism by which a deficiency causes the symptoms physical signs and functional and organic lesions that accompany that deficiency

The chemical nature biochemistry and physiology of thiamine have been described in detail elsewhere as has the chemical lesion of the deficiency [1] The effects of a deficiency are peripheral neuritis and congestive heart failure In addition to these clearcut unmistakable functional and structural disorders there are apparently disturbances in the psyche [2] and possibly in certain endocrine functions [3]

Pathologic Changes—The mechanism by which the chemical lesions of thiamine deficiency produce the structural changes in the peripheral nerves is unknown The lesion consists of a panneuritis beginning with

1 Handbook of Nutrition, to be published.

2 (a) Williams R. D Mason, H L. Power M. H and Wilder R M Induced Thiamine (Vitamin B) Deficiency in Man Relation of Depletion of Thiamine to Development of Biochemical Defect and of Polyneuropathy Arch. Int. Med. **71** 38 1943 (b) Hulse M C and others Subclinical Vitamin Deficiency Assay of Subclinical Thiamine Deficiency Ann. Int. Med. **21** 440 1944

3 (a) Musselman M M Nutritional Diseases in Cabanatuan, War Med. **8** 325 1945 Biskind M S Nutritional Deficiency in the Etiology of *Menorrhagia Metrorrhagia, Cystic Mastitis and Premenstrual Tension* Treatment With Vitamin B Complex, J Clin. Endocrinol. **3** [illegible]7 1943 (b) Klatskin, G Salter W T and Humm F D Gynecomastia Due to Malnutrition I Clinical Studies, Am. J M. Sc. **213** 19 1947 (c) Gynecomastia Due to Malnutrition II. *Endocrine Studies*, Am. J M Sc. **213**: 31 1947

degeneration of the myelin sheath and progressing to fragmentation of the axis cylinder and wallerian degeneration Special stains are needed to demonstrate best the earliest changes The process begins in the distal portions and the nerves of the lower extremities are ordinarily first affected In the beginning some fibers escape the number affected increasing with the duration and severity of the deficiency The cranial nerves including particularly the second, eighth vagus and phrenic and even those of the trunk may be affected[4] The sympathetic system is said to be involved In the central nervous system some degeneration of the sheaths of scattered fibers in the anterior and posterior nerve roots and posterior columns has been observed Changes in the cell bodies of the ganglions, anterior cells and medulla are reported and more recently, changes in and about the corpora mammillaria hypothalamus, thalamus the gray matter around the aqueduct, colliculi and floor of the fourth ventricle have been found These lesions consist of vascular dilatation, local hemorrhage and proliferation similar to that associated with superior hemorrhagic polioencephalitis (Wernicke's disease)[5]

Not only are these changes nonspecific but they have been ascribed by various writers to simple inanition and possibly to a deficiency or an associated deficiency of other vitamins such as pyridoxine[6] There seems little doubt however, that they can result from thiamine deficiency although all neuropathies of nutritional origin are not necessarily due to lack of thiamine

After treatment and recovery there is remyelinization and regeneration Many of the nerve fibers are restored to normal but the process is slow and lags behind symptomatic improvement Atrophy of the muscles innervated by the affected nerves occurs and the muscles show additional nonspecific microscopic changes, loss of striations and cloudy swelling or fatty degeneration of the fibers In some cases complete recovery may not occur and weakness and partial atrophy may remain as scars of the disease

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4 Spillane J D Nutritional Diseases of the Nervous System With a Foreword by George Riddoch Baltimore Williams and Wilkins Company 1947

5 Campbell A C P and Russell W R Wernicke's Encephalopathy Clinical Features and Their Probable Relationship to Vitamin B Deficiency Quart J Med **10** 41 1941

6 Wintrobe M M Miller M H Follis R H and Stein H J What Is the Antineuritic Vitamin? Tr A Am Phys **57** 55 1942

The heart shows dilatation and hypertrophy, notably on the right side and in the auricle There is hypertrophy of the wall of the right ventricle, which may be thicker than that of the left The cavity is enlarged, the valves are normal The conus arteriosus is dilated, according to Wenckebach[7] a peculiarity of the disease Histologically there is little but edema and some degeneration of the fibers The venous pressure is elevated

The exact nature of the enlargement of the heart is not known Its rapid disappearance under treatment suggests that it is not a true hypertrophy Selective localization of the enlargement is urged as evidence against edema as a cause for the enlargement or a direct action of thiamine on the heart muscle However variations in the concentration of the vitamin in different organs and tissues and in the accumulation of pyruvic acid suggest that local requirements may result in selective localization of the pathologic changes through an effect on the tissues themselves

Grossly and microscopically the edema, including hydrothorax hydropericardium and ascites shows nothing to distinguish it from the edema of ordinary congestive heart failure Chemically in the few studies made the edema fluid has been found to be low in protein and it has been suggested that the edema is not the result of increased venous pressure (congestive failure) alone but is due in part to other causes, either a specific effect of thiamine deficiency or, perhaps, hypoproteinemia Evidence against the former theory is the low protein content of the fluid which would rule out an effect of thiamine on capillary permeability However there remain other possible mechanisms such as an antidiuretic factor

In chronic cases there may be chronic passive congestion of the liver and other viscera and tissues Other changes such as hypertrophy of the islands of Langerhans the adrenal medulla and the thyroid and pituitary glands have been observed but no specific relation to thiamine is known Besides the structural changes there are functional abnormalities The circulation time is faster (shortened) despite the congestive failure There is an increased cardiac output a lessened arteriovenous

7 Wenckebach, K. F Der Mechanismus des plotzlichen Herztodes bei der Beriberi, Klin. Wchnschr 11 1641 1932

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4 Spillane J D Nut t onal Diseases of the Nervous System With a Forewo d by George Riddoch Baltimore Williams and Wilk ns Company 1947

5 Campbell A C P and Russell W R Wernicke s Encephalopathy *Clin cal Features and The r Probable Relationsh p to V tam n B Deficiency* Quart J Med **10** 41 1941

6 Wintrobe M M M ller M H Follis R H and Stein, H J What Is the Antineu tic Vitamin? T A Am Phys **57** 55 194-

vascular signs and symptoms and by edema, the dry form by peripheral neuritis, paralysis and atrophy of the muscles Beriberi can also be classed as acute or chronic. The acute form is most apt to be of the wet type and may suddenly appear during the course of chronic beriberi Infantile beriberi usually described separately is distinguished mainly by the age of the patient and the prominence of the wet or cardiovascular manifestations It is usually acute

In chronic beriberi which probably predominates in the sense that a rather long period of mild to moderate to increasingly severe symptoms usually precedes the development of more acute and disastrous signs, the onset is gradual. Actually this period represents a state of thiamine deficiency so-called subclinical deficiency or hypovitaminosis rather than classic beriberi

The principal manifestations of slight to mild deficiency or perhaps the earlier stages of more acute and severe deficiencies seem to be subjective and to consist of nervousness fatigability personality disturbances irritability moodiness depression and lack of initiative and interest. There may be poor powers of concentration and memory Experimentally these can be detected at first only by special tests [b] There is a shift in the personality type toward the psychoneurotic With these mental disturbances there may be gastrointestinal symptoms such as anorexia (not a prominent symptom in man and especially in children) indigestion gas and constipation. Circulatory symptoms include palpitation slight shortness of breath dizziness and, possibly slight edema. There may also be neurotic pains of various sorts weakness and heaviness of the legs stiffness cramps in the legs tenderness of the calves and paresthesias such as burning numbness and tingling of the feet and legs Burning and soreness of the feet seems to be a particularly troublesome and characteristic feature in some instances [11] although this may be due in part to a deficiency of other factors

Physical examination at this stage shows little. The subject may show some loss of weight. There may be tenderness of the muscles of the legs and areas of hyperesthesia or lessened superficial sensation. Vibratory sense and tendon reflexes may be diminished. There may be slight weakness of the legs Cardiovascular

[11] Hibbs, R. E. Beriberi in Japanese Prison Camps, Ann. Int. Med. 25 2 0 1946.

oxygen difference[8] an increased pulse pressure and a collapsing type pulse There is dilatation of the peripheral vessels

In actual pathologic deficiency the urinary excretion of thiamine is decreased[9] and an abnormal accumulation of pyruvic acid occurs, even in mild cases, under the influence of exercise or the intake of glucose With this there is a decrease in cellular and extracellular thiamine[2b] Symptoms of deficiency appear within a short time, perhaps ten days if the intake is reduced to zero and normal activity is maintained This is not a usual occurrence however, and ordinarily the process of the development of a real, pathologic deficiency is a slow one However a sudden, severe deprivation succeeding a long continued minimum intake can precipitate an acute deficiency even acute beriberi

Clinical Manifestations—The clinical manifestations of a slight or early deficiency are vague, variable and nonspecific The latter characteristic in fact, applies even to severe deficiencies There is nothing, structurally or functionally to distinguish neuritis due to thiamine deficiency from a good many other kinds of neuritides, except other evidence of thiamine deficiency Heart disease caused by beriberi as well as the signs and symptoms of it is similar to congestive heart failure of other origin and except when seen in pure form in regions where beriberi is common is difficult to distinguish from other similar kinds of heart failure[10]

This being true a recitation of the signs and symptoms of an early or mild deficiency has led to a misunderstanding of the actual frequency and importance of this deficiency Nervousness fatigability changes in disposition vague digestive disturbances anorexia, paresthesias arthritic pain and neuritic pain all occur with a thiamine hypovitaminosis but they also occur as the result of many other conditions

Clinically beriberi occurs in two rather distinct forms, the so called wet and dry though mixed cases are common The wet form is characterized by cardio

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8 Burwell, C S and Dexter L. Ber beri Heart Disease Tr A Am. Phys 60 59 1947

9 (*a*) Ruffin J M Cayer D and Perlzweig W A The Relation ship Between the Clin cal I ctu e of a M ld or E rly Vitamin Defic ency and Laborato y Determinat ons of Vitam n Levels Gastroenterology 3: 340 1944 (*b*) Hou H C The Di tary Intake and Urinary Output of Vitam n B and Their Relat on to Beriberi Among Ch ne e Chinese M J 61 6 1942 Hulse and oth s [b]

10 Blankenborn M A Diagnos s of Beriberi Heart D sease Ann. Int Med 23 398 1945

general atrophy and loss of weight reduces the patient to skin and bones" Foot drop may occur, with the characteristic steppage gait There is loss of deep sensation, with ataxia and loss of coordination of a peripheral type Contraction deformities may occur The milder mental symptoms of the early stage may be followed by mental confusion of the type seen in toxic infectious delirium Presbyophrenia (Wernicke's syndrome), confusion, ataxia and ophthalmoplegia may be associated with thiamine deficiency

The picture in wet beriberi is primarily that of congestive heart failure with edema or even anasarca a notable feature, but with certain important characteristics which help to distinguish it from the usual kinds of congestive failure The edema commonly begins in the legs and is most severe there being influenced by posture In severe cases there may be anasarca with ascites hydrothorax and hydropericardium With this there is shortness of breath palpitation and tachycardia of varying degree There may be precordial pain The pulse is notably labile and poorly sustained, and there is a considerable degree of peripheral dilatation There is exaggerated pulsation of the peripheral arteries The heart is enlarged usually greatest on the right and at the base because of enlargement of the conus There are numerous murmurs of a functional' type associated with dilatation The systolic blood pressure may be somewhat elevated but in uncomplicated cases not greatly and the diastolic pressure is normal or low, giving a large pulse pressure and a large poorly sustained pulse Often there is a pistol shot sound over the large peripheral arteries In contrast to ordinary congestive heart failure circulation time is decreased (faster) the arteriovenous oxygen difference is decreased, venous pressure is abnormally elevated and cardiac output is increased Electrocardiograms commonly show deviation of the RST segment lengthening of the Q T interval and diminution or inversion of the T wave in any or all leads Voltage is usually low None of these changes are specific but in uncomplicated cases they quickly revert to normal with adequate specific treatment Blankenhorn has noted several deviations from these observations [10] Features of particular value in diagnosis are (1) lack of other causes for the failure, (2) associated circumstances such as history of

changes are slight or absent There may be an otherwise unexplained tachycardia, an overactive heart, variable systolic murmurs, alterations in the character and intensity of the sounds and a slight elevation of the blood pressure The electrocardiogram is rarely helpful at this stage

However all these observations are vague, non specific, difficult to distinguish from variations within the normal range and only to be interpreted and evaluated in conjunction with all the other evidence which can be obtained As a result there has been a lamentable tendency too often to assume incorrectly the presence of a deficiency or failure to diagnose it when present The former is more frequent Only by painstaking attention to the details of history, to an analysis of symptoms and signs and to careful laboratory studies and by a critical interpretation of the therapeutic trial can the true deficiencies be separated from the imitation This may be extremely difficult and few are willing to do it Many physicians merely make a presumptive diagnosis and give empiric treatment with the vitamin If however one is disposed to use care and the available aids, diagnosis can be made with fair accuracy

Depending on the degree and progressive nature of the deficiency these manifestations may remain more or less constant, fluctuating from time to time with the intake of the vitamin If they progress after a variable period, depending on the severity of the deprivation and the precipitating factors, the major symptoms and signs develop As indicated earlier this may occur when a sudden further sharp decrease in the intake of the vitamin occurs in a person who has had a continuous slight deficiency When these symptoms develop rapidly they of course indicate that the condition is acute but most acute cases occur against the background of a relatively long period of mild disease

In dry beriberi the symptoms and physical signs are those of a peripheral neuritis which nearly always begins distally, in the feet and legs The early symptoms of weakness pain tenderness of nerve trunks and paresthesias are followed by actual paralysis atrophy of muscles anesthesia and loss of deep reflexes and vibratory sense Extensive atrophy makes the legs appear as mere sticks unless the loss is hidden by edema As the disease progresses the upper extremities and trunk may be affected including even the diaphragm and a

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dietary defects or alcoholism (3) the labile pulse, (4) more rapid circulation (decreased circulation time) in the presence of failure, (5) evidence of failure on both the right and left sides with enlargement more often on the right, (6) large pulse pressure, (7) prominent edema and (8) failure of response to usual treatment (digitalis) Electrocardiographic changes occur but are not diagnostic The occurrence of this condition in infants should be remembered

Patients with mild chronic beriberi of the wet, or cardiovascular, type and also those with the neuritic form are subject to acute congestive failure and collapse with pulmonary edema enlargement of the liver severe dyspnea cyanosis falling blood pressure peripheral stasis and death Such conditions, developing after few previous symptoms, constitute the acute or malignant form of beriberi

So called infantile beriberi is really such an acute form with cardiovascular symptoms predominating It occurs principally during the first few months of life and is characterized in the beginning by anorexia, regurgitation abdominal distention, tenderness and colicky pain Vomiting and constipation may follow There is oliguria and later, edema which masks a loss of weight Dyspnea and tachypnea appear and there is a peculiar cry or grunt said to be caused by edema of the vocal cords Later signs of congestive failure increase The heart becomes enlarged (right side) and cyanosis and pulmonary edema appear The edema becomes extensive with effusions into the serous sacs Still later there are nervous and mental symptoms signs of increased intracranial pressure meningism muscular twitching drowsiness coma and death True convulsions are uncommon but rigidity is not infrequent In the adult mixed cardiovascular and neuritic types of beriberi are common

Besides the neuritic and cardiovascular symptoms and physical changes there may be a number of other changes The anorexia of a mild deficiency may be succeeded by nausea and vomiting So called indigestion is common as is constipation Roentgen examination shows loss of haustrations diminished intestinal tone and decreased motility although a spastic colon has been described *In severe cases involvement of the* optic nerve with amblyopia optic neuritis some papilledema and optic atrophy may occur [4] Similarly, the

eighth nerve may be affected, with resulting tinnitus and deafness An unusual number of such cases were seen among American prisoners of war in Japanese prison camps Whether the testicular atrophy, gynecomastia and skin rash observed under these conditions [12] were an expression of the beriberi (thiamine deficiency) or whether they were from some other cause is not known but the response to treatment including administration of single vitamins in pure form, makes it possible The same is true of amenorrhea in women under similar circumstances

Diagnosis—Diagnosis is based on the knowledge of a deficient diet the presence of the symptoms and physical signs described laboratory tests and a therapeutic trial Of all the laboratory tests the tests of the excretion of vitamin B_1 (thiamine) are for the present the most useful Several methods for the determination of thiamine excretion are available, of these the various modifications of the thiochrome technic are probably the most suitable for clinical work The determination of the amount excreted in one hour with the patient in the fasting state has been rather widely used [13] but twenty four hour excretion has also been employed [14] A variety of load tests have been proposed [15] one fairly commonly used being the measurement of the output in four hours after the administration of 5 mg of thiamine hydrochloride by mouth [16] With this procedure an output of less than 20 micrograms (0 02 mg) is considered subnormal There is no single, generally accepted standard for such tests

12 Ruffin Cayer and Perlzweig [8a] Klatskin Salter and Humm [3b]

13 (a) Johnson R E Henderson C R Robinson P F and Consolazio F C Comparative Merits of Fasting Specimens and Oral Loading Tests in Field Nutritional Surveys J Nutrition 30 89 1945 (b) Oldham H G Davis, M V and Roberts L J Thiamine Excretions and Blood Levels of Young Women on Diets Containing Varying Levels of B Vitamins With *Some Observations* on Niacin and Pantothenic Acid J Nutrition 32 163 1946 (c) Holt L E Jr and Najjar V A A Simple Method for the Laboratory Diagnosis of Subclinical Deficiencies of Thiamine Riboflavin and Nicotinic Acid Bull. Johns Hopkins Hosp 70 329 1942 Papageorge E. and Lewis, G T A Study of the Fasting Hour Excretion of Thiamine in the Urine of Normal Subject J Nutrition 34 301 1947

14 Youmans J B and Patton E. W The Laboratory Diagnosis of Nutritional Deficiencies Clinics 1 303 194

15 Melnick D and *Field H Jr* Thiamine Clearance as an Index of Nutritional Status J Nutrition 24 131 1942 Ruffin J M Cayer D and Perlzweig W A The Relation Between the Clinical Picture of a Mild Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels Gastroenterology 3: 340 1944 Oldham, Davis and Roberts [13b]

16 Johnson R E. Sargent F Robinson P F and Consolazio, F C. Assessment of Nutritional and Metabolic Condition in the Field General and Clinical Aspects War Med. 7: 427 1945 Goldsmith, G A. and Sarett, H P *Urinary* Excretion of B Vitamins in Persons on Normal and Restricted Diets Federation Proc. 7 288 1948

Despite arguments as to the exact normal excretion or the response to a test dose, a zero or near zero excretion and little or no response to a test dose is prima facie evidence of poor intake which probably has existed long enough that some deficiency is present Even within these limitations such a test is useful clinically and may yield significant evidence before more obvious signs are present on physical examination or from symptoms Increases of the same relative magnitude in the concentration of pyruvic acid in the blood are probably equally significant in the absence of other causes for the increase in the pyruvate Determination of the concentration after a standard exercise test or after the administration of glucose is preferable It is helpful to determine the concentration of lactic acid simultaneously [17]

Finally, there is the response to specific treatment Failure to respond promptly and fully to adequate treatment with thiamine except for those changes (paralysis, weakness and atrophy) which may be permanent effects, or scars, of the disease is rather conclusive evidence against a diagnosis of thiamine deficiency

Reference has already been made to the milder cases or those more recent and of shorter duration, and the inadequacy of diagnosis There will be few, if any, definite signs Laboratory tests will be equivocal Symptoms will be vague and variable Dependence in diagnosis must be placed on the establishment of a possible deficient intake relative or absolute, a possible difficulty of absorption and utilization ultimately and, above all the therapeutic trial even though a slender reed on which to lean

Incidence —It is impossible to give a reliable estimate of the incidence of thiamine deficiency in this country Actual beriberi is uncommon although occasional sporadic cases are encountered usually in association with other diseases especially alcoholism [18] The wet, or cardiovascular type seems to be more common Blankenhorn [10] proved 12 such cases and some years ago Weiss reported the rather frequent occurrence of such cases in Boston In general his experience has not been duplicated elsewhere The incidence of hypo

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17 Goldsmith G A. The Blood Lactate-Pyruvate Relationship in Various Physiologic and Pathologic States Am J M Sc **215** 18? 1948

18 Weiss S., and Wilkins R. W The Nature of the Cardiovascular Disturbance in Nutritional Deficiency States (Beriberi) Ann Int. Med. **11** 104 1937

vitaminosis deficiency states short of beriberi has undoubtedly been exaggerated because of uncritical acceptance of minor and nonspecific signs and symptoms as indicative of the disease On the other hand there is undoubtedly a certain persisting amount of the deficiency among those elements of the population which are usually, but not always conditioned by economic factors or other disease In many places particularly the Pacific and the Far East thiamine deficiency and beriberi are rampant. An interesting survey of the incidence of beriberi in such a region—Bataan—has recently been reported[19] In the Philippines beriberi ranks a close second to tuberculosis as a cause of death.

Treatment —Treatment is simple and consists of the administration of a sufficient amount of the vitamin to relieve the deficiency and the symptoms quickly the restoration of body stores and the provision for the maintenance of a continuing adequate intake In mild or early cases this is best done with a diet rich in thiamine. Such treatment will supply sufficient of the specific vitamin and has the added advantage of providing other nutrients which are often lacking as well as establishing proper dietary habits to prevent recurrences

In more severe cases or in cases in which larger doses or parenteral administration are needed the pure vitamin is given Ordinarily it should be used alone especially in mild or doubtful cases so it can serve as a therapeutic trial or a test of the diagnosis. Large amounts are rarely if ever needed Doses in excess of 10 to 20 mg daily are lost in the urine [20] The loss is relatively more rapid and greater if the thiamine is given parenterally Parenteral use should be confined to those cases in which administration by mouth or absorption from the gastrointestinal tract is impossible impractical or in doubt. The only indication for large doses more than 20 mg daily is in conditions such as optic neuritis in which there is need to secure maximum benefit with the greatest speed to prevent or minimize permanent injury Even in such cases it is doubtful whether more than a few milligrams are utilized Treatment should

19 Salcedo J., Jr Carrasco, E. O Jose F R., and Valenzuela, R. C. Studies on Beriberi in an Epidemic Sub-Tropical Area, J Nutrition 36 561 1948

20 Freidemann, T E. Kmieciak T C Keegan, P K. and Shift, B B The Absorption, Destruction and Excretion of Orally Administered Thiamine by Human Subjects, Gastroenterology 11 100 1948.

be continued until recovery is complete or until maximum benefit is gained, but, in any event, proper diet whenever possible, should be added to supplement the pure vitamin Concentrates such as yeast, wheat and corn germ and preparations of rice polishings are useful as supplements to food or thiamine or as "in between" preparations in treatment Suitable yeasts should be used

Patients with beriberi, particularly the wet form, should remain in bed to lessen the likelihood of cardiovascular collapse and to lessen the symptoms In acute heart failure venesection may be an immediate life saving measure Digitalization is usually not effective Diuretics may be used temporarily to relieve edema, but the effect of thiamine is about as rapid Rest is also desirable for the neuritis Analgesics, even codeine and morphine, may be required for pain but should be discontinued as soon as possible Pain may be severe and persistent even after treatment Concurrent disease must of course be treated and conditions responsible for improper intake absorption or utilization relieved whenever possible Particular attention should be paid to preventive measures in those unusually liable to deficiencies such as pregnant and nursing women, persons with alcoholism, patients with nervous and mental diseases patients on restricted diets and patients with illnesses which interfere with intake and absorption

RIBOFLAVIN

The first clinical description of riboflavin deficiency as such in man was the result of observations made on a group of experimental subjects deliberately provided a diet deficient in that nutrient [21] After ninety four to one hundred and thirty days of such a diet, pallor of the mucosa of the lip at the angle of the mouth followed by maceration and superficial transverse fissures developed in 10 of the 18 subjects The lips became abnormally red at the line of closure There was a fine scaly slightly greasy desquamation on an erythematous base in the nasolabial folds on the alae nasi in the vestibules of the nose and on the ears Similar lesions had been described in persons with pellagra by Goldberger and

21 Sebrell W H and Butler R E. Riboflavin Deficiency in Man Pub Health Rep 53: 2282 1938 Kruse H D, Sydenstricker V P Sebrell W H and Cleckley H M Ocular Manifestations of Ariboflavinosis Pub Health Rep 55 157 1940

Tanner,[22] Wheeler[23] and Stannus[24] and attributed to a deficiency of vitamin B_2. The lesions were described in persons who did not have pellagra by Landor and Pallister[25] and Aykroyd and Krishnan.[26] Later, other lesions of the skin, glossitis and ocular changes were described as occurring with this deficiency.

Since that time these signs have been rather generally accepted as manifestations of riboflavin deficiency, but in the last few years there has been a considerable change in ideas with respect to their specificity. Many now believe that while most, if not all, the changes originally described can and do result from riboflavin deficiency, they can be and are the result of other causes and hence are not pathognomonic. Diagnosis, as is so often the case with nutritional deficiencies as well as with other diseases, requires additional and supporting evidence. This is particularly true of mild or early lesions.

Basically, a deficiency of riboflavin interferes with the formation of a number of flavoproteins which function as enzymes in the important process of tissue respiration. The manner in which this causes the abnormalities in the tissues which are the bases of the clinical expressions of the deficiency is unknown. The similarity of the pathologic changes to those seen in pellagra, the circumstance that niacin is involved in a similar cell respiration enzyme and the common occurrence clinically of riboflavin deficiency with pellagra lead to the speculation that the change in the tissue is the result of a basic alteration in cellular physiology in certain tissues which can be induced by any one of several defects in enzyme formation and function. This view is supported by observations that other vitamins, whose significance for man has not yet been established, have at times been described as being

22 Goldberger, J., and Tanner, W. F.: A Study of the Pellagra Preventive Action of Dried Beans, Casein, Dried Milk and Brewer's Yeast, With a Consideration of the Essential Preventive Factors Involved, Pub. Health Rep. 40: 54, 1925.

23 Wheeler, G. A.: The Pellagra Preventive Value of Autoclaved Dried Yeast, Canned Flaked Haddock, and Canned Green Peas, Pub. Health Rep. 48: 67, 1933.

24 Stannus, H. S.: Pellagra in Nyasaland, Tr. Roy. Soc. Trop. Med. & Hyg. 5: 112, 1912.

25 Landor, J. V., and Pallister, R. A.: Avitaminosis B_2, Tr. Roy. Soc. Trop. Med. & Hyg. 29: 121, 1935.

26 Aykroyd, W. R., and Krishnan, B. G.: Stomatitis Due to B_2 Deficiency, Indian J. M. Research 24: 411, 1936.

27 Deleted in proof.

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21 Seb ell W H and Butler R E R boflavin Defic ncy n Man Pub Health Rep 53 2?8~ 1938 Kru e H D Syd nstricker V P Sebrell W H and Cleckley H M Ocular Manifestations of Ar boflavinos s Pub Health Rep 55 157 1940

of the cornea (vascularization) can be detected with any certainty only with the use of the large slit lamp As a matter of fact, in earlier reports many conditions reported as vascularity of the cornea were not true, pathologic vascularization

Actually, the first reports of the lesion in riboflavin deficiency give a clear and correct description of the true lesion[32] but unfortunately this description was subsequently not fully understood or was misinterpreted, which led to deviation from the original concept and to errors in diagnosis

Briefly, there is an actual vascularization of the cornea with penetration by capillaries from the limbic plexus, which in advanced cases invade the entire cornea In the beginning there is congestion and proliferation of the limbic plexus Following and accompanying this narrow capillary loops appear at the edge of the scleral digitations Next there is actual invasion of the cornea by capillaries arising from scleral loops These are usually best seen in the nasal and inferior quadrants and lie just below the epithelium of the cornea. It is of primary importance and significance that this be an actual invasion of the cornea not just a proliferation or filling of capillaries at the sclerocorneal junction Failure to understand or heed this fact *has led to confusion and is largely responsible for* the false reporting of many instances of vascularization and riboflavin deficiency Mere circumcorneal injection occurs with no relation to riboflavin deficiency, as can vascularization of the cornea but other causes can be more readily eliminated if there is vascularization, and it is more significant of true riboflavin deficiency The distinction between mere circumcorneal injection and filling and proliferation of capillaries at the sclerocorneal junction can be easily made with the proper instruments (slit lamp), technic training and experience It is important that the existence of a normal avascular zone between the limbic plexus and the sclerocorneal junction be doubtful[33]

As the lesion progresses deeper invasion occurs, until finally in advanced cases, general vascularization

32 Sydenstr ker V P Sebrell W H Cleckl y H M and Kruse H D The Ocular Manifestati ns of Ar boflavin s s A Progress Note, J A. M A **114**:2437 (July 22) 1940 Ocular Manif stations of Ar boflav no s Pub Health Rep **55** 157 1940

33 Va l D and Ascher K. W *Corneal Vascularization Problems*, Am J Ophth, **26** 1025 1943

related, usually in the way of causing improvement or cure of pathologic processes and symptoms similar to those seen in both riboflavin deficiency and pellagra.

Although a variety of lesions are described in animals, nothing is known in man of the pathologic changes caused in the tissues by riboflavin deficiency, except for the gross appearance of the lesions of the skin, mucous membranes and eyes and the microscopic changes in the eye (corneal vascularization) The former are described in the portion on clinical manifestations In rats some disturbance in water metabolism apparently occurs in riboflavin deficiency [28] and its prevention with cortical hormones (adrenal) as well as with riboflavin suggests a possible relation to the sudden collapse and death which can occur in riboflavin deficient animals Whether any similar effects occur in man is unknown

By far the most frequently reported manifestation of riboflavin deficiency has been vascularization of the cornea The incidence of this abnormality attributed to a shortage of riboflavin, has been reported to be as high as 75 8 and 99 5 per cent in some groups [29] As has already been stated however it is realized that this abnormality is not specific and apparently occurs rather frequently as the result of a number of other nutritional disturbances, as well as other conditions Some have reported as few as 31 cases of the lesion in 1 059 patients [30] Furthermore, it has become clear that there has been a great deal of misunderstanding of the nature of the vascularization There has been failure to understand or recognize that true vascularization implies an actual invasion of the cornea by new capillaries and that pericorneal injection and hyperemia alone do not of necessity mean vascularization of the cornea although they may be associated with it Finally it has become clear that to be significant there must be an actual definite invasion of the cornea [31] and that actual invasion

28 Gaunt R Liling M and Mushett C W Disturbances of Water Metabolism in Vitamin Deficiencies and Effects of Adrenal Cortical Hormones Endocrinology **38** 127 1946

29 Wiehl D G and Kruse H D Medical Evaluation of Nutritional Status Prevalence of Deficiency Diseases in Their Sub-Clinical Stage Milbank Memorial Fund Quarterly **19** 241 1941 Tisdale F F, McCreary J F and Pearce H The Effect of Riboflavin on Corneal Vascularization and Symptoms of Eye Fatigue in R. C A. F Personnel Canad M A J **49** 5 1943

30 Gregory M K The Ocular Criteria of Deficiency of Riboflavin, Brit M J **2** 134 1943

31 Mann I Ariboflavinosis Am. J Ophth. **28** 43 1945

phobia burning itching and visual disturbances may disappear or greatly lessen The circumcorneal injection decreases and the capillary loops begin to empty Superficial opacities clear up sooner than the deeper interstitial nebulae and the posterior opacities are the last to disappear Later all the signs except for possible permanent injury from infection disappear The empty capillaries may remain a long time and some of them at the sclerocorneal junction appear to be permanent [32] Inasmuch as the course of the disease may be irregular with alternate improvement and worsening particularly under natural conditions there may be recurring partial or complete return of symptoms and lesions again followed by improvement.

The second most common lesion found in riboflavin deficiency appears to be *cheilosis* *This is manifested* in two ways first by a general inflammation of the mucous membrane and mucocutaneous border of the lips and second by maceration and fissuring at the corners of the mouth The inflammation of the lips is noninfectious and resembles the stomatitis or even the dermatitis that occurs with pellagra The lips are swollen, sometimes sore and burning and either redder than normal or a grayish red because of a thin overlay of grayish desquamated epithelium When this is removed the reddening of the mucous membrane is revealed. Occasionally there is an actual shallow ulceration with a thin exudate pseudomembrane or crusting The changes often extend well into the buccal mucosa in the more severe cases Some writers speak of a fine wrinkling of the vermilion border as a sign of this cheilosis but I would question its significance

The lesions at the corners of the mouth consist of maceration and whitening of the skin at the angles followed by the appearance of radiating reddened fissures beginning as mere moist reddened streaks They are often covered with a thin slightly yellow crust or exudate which is easily removed and does not leave a bleeding surface although the reddening and depth of the fissure becomes more apparent Often there is an extension of the redness to the buccal mucosa just inside the mouth

Again these lesions are not specific for riboflavin deficiency [35] They are found in persons with dental

35 Finnerud, C W Perleche Its Nosologic Status, J A M A 126 737 (Nov 18) 1944

develops Anterior (superficial) vascularization is greater than posterior in riboflavin deficiency, in contrast to greater posterior vascularization in syphilitic interstitial keratitis With more severe vascularization, opacities occur, first as superficial nebulae with slight "steaminess" and later as more dense and deeper lesions Superficial punctate opacities and posterior opacities are less common

Sydenstricker and associates[32] recognized and pointed out that other causes for the vascularity exist, as, for example, syphilis although there were certain features which were helpful in differentiation It was apparently not realized at that time however, how frequently a mild vascularization could arise from other, relatively minor causes, including even mild trauma to the cornea Finally it appears that in animals at least corneal vascularization results from a deficiency of any *one of* the essential amino acids and, hence, in some circumstances from a deficiency of protein itself[34]

In addition to the invasion of the cornea by capillaries, there are other ocular signs and symptoms There is usually *conjunctivitis often with* blepharospasm There is increased lacrimation in sharp contrast to all but the earliest stages of the conjunctivitis caused by vitamin A deficiency Accompanying the conjunctivitis and vascularization of the cornea when they are present is circumcorneal injection which has been interpreted as evidence of an involvement of the uveal tract uvea, iris and ciliary body Changes in the pigment of the iris have been described and there may also be mydriasis Unfortunately the circumcorneal injection has often been considered an indication of or has mistakenly been considered to be corneal vascularization and has by itself been considered a sign of a deficiency of riboflavin Actually it is commonly the result of mild trauma or glare and dust with and without corneal vascularity or riboflavin deficiency With the ocular *changes there is a disturbance of vision, principally* a sense of cloudiness or dimness of vision and a decrease in visual acuity In severe cases there may be ulceration of the cornea and secondary infection

The symptoms and lesions in the eye change rapidly under treatment Within a day or two the photo

34 Sydenstricker V P Schmidt H L and Hall W K The Corneal and Lenticular Changes Resulting From Amino Acid Deficiencies in the Rat. Proc. Soc. Exper Biol. & Med. 64 59 1947

general they are not relieved by administration of niacin alone, but their improvement or disappearance following treatment with other members of the vitamin B complex suggests that they can result from deficiencies of those vitamins as well as from deficiency of riboflavin

Diagnosis — Aside from the presumptive evidence of a deficient food intake, the diagnosis of riboflavin deficiency is based on the presence of symptoms and lesions of the disease with some assistance from laboratory tests of the excretion of riboflavin As is the case with nonspecific changes a therapeutic trial is almost essential in the interpretation and evaluation of the signs

Diagnosis of the deficiency before the physical manifestations appear is almost impossible although a suggestion can be gotten from the diet record and the excretion test might offer some supporting evidence By the time symptoms such as burning of the tongue and eyes dimness of vision photophobia and lacrimation appear, physical signs are already present Gross inspection will reveal conjunctivitis photophobia lacrimation and blepharospasm, however in order to detect some degrees of circumcorneal injection and always to detect true capillary invasion of the cornea one must use a slit lamp (large model) With such an instrument invasion is easy enough to detect, if it is present

The only laboratory test in common use is a test of the urinary excretion of the vitamin spontaneous or following administration of a test dose Both microbiologic[40] and fluorometric[41] methods have been used for the determination of riboflavin and a microtechnic is available[42] Determination of the excretion in one hour with the patient fasting or several hours after an oral or parenteral test dose is administered has been employed most often As in the case of thiamine the normal limits are not clearly established Excretion while the patient is fasting of less than 20 micrograms (0 02 mg) per hour has been suggested as the lower normal limit and 200 micrograms (0 2 mg) is the

40 Snell E E and Strong F M A Microbiological Assay for Riboflavin Indust. and Engin. Chem (Analyt. Ed.) 11 346 1939

41 Ferrebee J W Urinary Excretion of Riboflavin Fluorometric Methods for Its Estimation J Clin Investigation 19 51 1940 Najjar V A Fluorometric Determination of Riboflavin in Urine and Other Biological Fluids J Biol Chem. 141 355 1941

42 Bessey O A. and Lowry O H Biochemical Methods in Nutritional Surveys Am. J Pub. Health 35 941 1945

plates (false dentures)[36] and can occur with an iron deficiency[37] Occasionally they appear to be due to neither riboflavin nor iron deficiency and seem to respond to one or another of the other members of the vitamin B complex[38] or to crude mixtures such as crude liver extract or dried yeast, which presumably represents most or all of the vitamin B complex

The other buccal lesion ascribed to riboflavin deficiency is glossitis Considerable dispute has arisen regarding this manifestation The tongue in riboflavin deficiency was originally described as purplish or magenta in color without a coat The fungiform papillae are said to be affected principally and are flattened and slightly enlarged There is no atrophy[39] There is, sometimes soreness and burning of the tongue It has been difficult for many observers to distinguish this glossitis from those associated with other nutritional deficiencies, and the lesion has not always shown the response to specific treatment which should have resulted if it had been caused specifically by a lack of riboflavin[38]

The dermatitis of riboflavin deficiency is essentially a seborrheic dermatitis, with fine greasy scales on a slightly reddened base It is most common about the nose in the nasolabial and nasomaxillary folds on the cheeks and on the chin A somewhat similar lesion, but usually with more crusting has been described on the lobes of the ear, especially posteriorly, and Sydenstricker and his associates described a similar dermatitis on the hands

All the generally accepted lesions of riboflavin deficiency with the possible exception of the ocular lesions have in the past been seen most often in association with pellagra Whether they are to be considered a part of the pellagra syndrome or a complicating riboflavin deficiency is uncertain but most observers are of the opinion that when they accompany pellagra they are the expression of a complicating riboflavin deficiency In

36 Ellenberg M and Pollack H Pseudo Ariboflavinosis J A. M. A. **119** 790 (July 4) 1942

37 Darby W J The Oral Manifestations of Iron Deficiency J A M A **130** 830 (March 30) 1946

38 Machella T E Studies of B Vitamins in Human Subject The Response of Cheilosis to Vitamin Therapy Am J M Sc **203** 114 1942. *Cayer D Ruffin J M and Perlzweig W A The Clinical Significance* of Glossitis and Cheilosis in Deficiencies of the B Complex South M J **38** 111 1945

39 Jeghers H Nutrition The Appearance of the Tongue as an Index of Nutritional Deficiency New England J Med. **227** 221 1942 or Nutrition Rev **1** 116 1943 Sebrell and Butler[a]

evidence Certainly the incidence is nowhere near as high as the 99 5 per cent reported by some observers in special groups even in those groups [9] On the other hand it is possibly higher than is suggested by other studies [44] As is usually the case the highest incidence is to be expected in generally poorly nourished groups or populations For this reason it might be expected to be high among the large masses of poorly nourished persons in such countries as India and countries in Africa. Reports of a high incidence among those peoples are probably more or less correct In this country it is most likely to be found as a conditioned deficiency associated with other disease including other deficiency disease which has induced the riboflavin deficiency Groups which are poor economically are of course more liable to the condition Some indication of incidence in one age group is found in a survey of soldiers presumably healthy, approximately 6 per cent of whom showed nonocular signs possibly representing riboflavin deficiency [47] None showed vascularization of the cornea Of a general population in Tennessee some 8 per cent had physical signs which might be indicative of riboflavin deficiency [48] On examination with the large slit lamp none had vascularization of the cornea.

Treatment—Treatment is ordinarily simple and consists of the administration insuring proper absorption of an adequate amount of the vitamin In mild cases this can be done simply with a diet of foods such as milk eggs and liver rich in riboflavin or with concentrates such as yeast and crude liver extract In many cases however, it will be best to begin with a suitable pharmaceutic preparation Such treatment should always be accompanied and followed if possible with administration of concentrates and proper diet the latter to be continued Ordinarily 5 to 10 mg of riboflavin a day will suffice but in some cases especially in cases in which there may be difficulty in absorption or utilization larger doses may be needed The oral route is ordinarily satisfactory but parenteral routes may occasionally be necessary to insure absorption or utilization

47 Youmans J B Deficiencies of the Fat Soluble Vitamins, J A M A 144 34 (Sept. 2) 1950
48 Youmans, J B Unpublished data.

lower normal limit in four hours after administration of a test dose of 5 mg[43] by mouth A good summary of the various tests is presented in a recent bulletin of the National Research Council[44] Since a low excretion may exist for some time before a true pathologic state occurs, a low or zero excretion is not of itself certain evidence of the presence of actual disease Nevertheless, a zero or near zero daily excretion or the lack of a significant response (increase) to a test dose is highly suggestive evidence of depleted body stores and a threatened or actual deficiency disease state[45]

All the symptoms and lesions should respond promptly to treatment with riboflavin either in pure form or in mixtures concentrates or food, if the dose is adequate Similarly, the urinary excretion should rise Failure to respond should be considered strong evidence against the diagnosis of riboflavin deficiency and such confirmatory therapeutic tests should be used in doubtful cases For this purpose pure preparations of riboflavin should be used The response of the vascularization of the cornea to treatment consists of an emptying of the capillaries with gradual collapse and perhaps partial disappearance If treatment is discontinued before a cure is secured the empty vessels refill Such a response and relapse may be used as a diagnostic aid This may be especially helpful in distinguishing between vascularization caused by riboflavin deficiency and that resulting from amino acid deficiency or other causes The possibility that riboflavin deficiency is the cause of the ocular manifestations of acne rosacea seems to have been disproved[46] although riboflavin deficiency could occur in a patient with this disease

Incidence—It is practically impossible to give any over-all figure for the general incidence of ariboflavinosis particularly in view of the confusion and uncertainty concerning the relative specificity of the various symptoms and lesions which have been reported and the doubt which has been cast on reported incidences based on surveys using these symptoms and signs as

43 Johnson R E Sargent F Robinson P F and Consolazio F C Assessment of Nutritional and Metabolic Condition in the Field General and Clinical Aspects War Med 7 7 1945

44 Nutritional Surveys Their Techniques and Value National Research Council Bulletin No 17 Washington D C May 1949

45 Holt L E Jr Exhibit New York Academy of Medicine Post Graduate Fortnight October 1947

46 Fish M Acne Rosacea Keratitis and Riboflavin (Vitamin B₂) Brit J Ophth **27** 107 1943

cystic crypts of Lieberkühn, give a stippled appearance to the mucosa a condition said by Herzenberg[51] to be found only in pellagra and sprue Later there is atrophy of the mucosa None of these would seem to be early lesions according to present concepts of the deficiency Scattered degeneration of axis-cylinders of the pyramidal cells of the cortex and myelin degeneration of fibers in the spinal column mostly the posterior, is found This degeneration appears to be related to the deficiency of niacin Peripheral lesions are uncommon and when present are probably the result of other deficiencies as are the other neurologic lesions None of the lesions of the nervous system is specific

Functionally there is a great reduction in the urinary excretion of N methylnicotinamide one of the forms in which niacin is excreted when the intake is greatly reduced[52] and hence presumably in cases of niacin deficiency This effect is the basis for laboratory tests of the deficiency

Numerous other pathologic changes are found in pellagra many of which—cheilosis, corneal vascularization gingivitis and peripheral neuritis—are undoubtedly the result of other nutritional deficiencies Other changes may be related to the niacin deficiency itself but are variable in occurrence and degree and may also be related to other deficiencies or to various combinations of deficiencies Included in this category[53] are gastric hypoacidity and anacidity with decrease of Castle s intrinsic factor An anemia which is often macrocytic and possibly related to the changes in the gastric juice or microcytic and possibly the result of an associated iron deficiency or directly related to the lack of niacin[54] is common

Pellagra itself is too well known to require extensive description here Such monographs as that of Harris[55] provide a full discussion The characteristic features are dermatitis glossitis stomatitis proctitis vaginitis and mental changes Acute and chronic forms occur and relapses and remissions are common The derma

51 Herzenberg H Pellagra (pathologisch anatomische Studien) Beitr z. path Anat. u allg Path 96:97 1935

52 Briggs A P Singal S A and Sydenstricker V P Study of Nicotinic Acid Restriction in Man J Nutrition 29:331 1945

53 Sydenstricker V P and Armstrong E. S Review of 440 Cases of Pellagra Arch Int. Med 39 883 1937

54 Wintrobe M Clinical Hematology ed. 1 Lea & Febiger Philadelphia 1942 p 33

55 Harris S Clinical Pellagra St. Louis C. V Mosby Company 1941

NIACIN

The well known disease, pellagra, can be assumed for present purposes to be the principal manifestation of a severe deficiency of niacin There are however less severe degrees of niacin deficiency, and the symptoms and signs of such mild or early deficiency, sometimes called pellagra sine pellagra, are naturally related to the same tissues and organs as are affected in frank pellagra

The *chemical nature, function and other characteristics* of niacin have been discussed elsewhere[1] The chemical lesion which results from a deficiency of the vitamin is an interference with the formation and presumably the function of the respiratory enzymes, diphosphopyridine and triphosphopyridine nucleotide, of which niacin is an essential part but how this is concerned with the lesions of the deficiency other than through a general interference with cellular metabolism *is not known*

The gross and microscopic changes in the tissues in pellagra and niacin deficiency are notably lacking in any peculiar characteristics and are, in general the simple, nonspecific type seen in a variety of inflammatory processes In actual pellagra however, the sum of the changes is sufficient to permit a pathologic diagnosis of the disease The gross changes are those described in the portion on clinical manifestations *Microscopically there are some lesions in the skin* and colon which Denton[49] Eddy and Dalldorf[50] hold to be characteristic in the early stages They consist of edema of the papillae, dilatation of the papillary blood vessels and deterioration of the superficial fine collagen layer of the corium Later, the capillary epithelium is swollen and the finer collagen fragmented Vesicles form and become infected and sloughing of the epidermis ensues Later the superficial layer may be *either atrophied or thickened* The *nature* of the increase in pigment is unknown In the oldest lesions there is atrophy of the rete mucosum and a thin epidermis

The walls of the colon are thickened and inflamed, with patches of pseudomembrane Small gray bodies,

49 Denton J Pathology of Pellagra J Trop Med 5:173 1925
50 Eddy W H and Dalldorf G The Avitaminoses The Chemical Clinical and Pathological Aspects of the Vitamin Deficiency Diseases, ed. 3 Baltimore Williams & Wilkins Company 1944

Although they fail to present the characteristic picture of pellagra, the symptoms and signs of mild niacin deficiency, or pellagra sine pellagra, are naturally related to the same tissues and organs as are affected in frank pellagra They are, principally the mucous membrane of the gastrointestinal tract, the vagina, the rectum the skin (especially in the exposed areas) and the central nervous system There are usually general signs of undernutrition and lack of energy, in *spite of seeming good health* ' *Other lesions* as is true in frank pellagra, are probably those of associated deficiencies

The symptoms and signs related to the gastrointestinal tract are a sore mouth mild diarrhea, slight proctitis, anorexia and indigestion None are severe The sore mouth is the result principally of glossitis and sometimes of mild stomatitis and pharyngitis Stomatitis without clearly defined glossitis is unusual In mild or slight glossitis the tongue is reddened usually only at the tip and sides with some atrophy of the papillae, as a rule In chronic cases there may be some general atrophy of the tongue The proctitis is often noticed only on examination The diarrhea is inconstant and mild often with only three to four stools a day, without any outstanding characteristics of the feces The stools may however sometimes be watery and more frequent than is normal The significance of the diarrhea is often attested by the results of the therapeutic trial The indigestion is vague and indefinite

The dermatitis is often lacking altogether especially in the acute or recent type When present it is seldom of the acute bright red diffuse inflammatory sunburn type of dermatitis That apparently is reserved for acute and severe forms of the deficiency occurring in *conjunction with at least a moderate exposure to light* In the milder form, especially in the milder chronic form there may be a slight dull reddening of the skin of exposed areas ordinarily the backs of the hands and the neck sometimes the dorsum of the foot The lesions are symmetric but often the borders are ill defined There is roughness some thickening and slight crusting Unexposed areas which seem to be affected at times are the elbows knees and scrotum Thinning and atrophy of the skin and subcutaneous tissues, espe-

titis is bilaterally symmetric and is more frequent and usually more severe on the exposed areas the face neck, hands, forearms and feet however, in the more severe forms of the disease it can be found in protected areas, even in such places as the scrotum Sunlight precipitates and intensifies the lesions, as do other traumas, such as heat and friction The lesion is inflammatory in nature and in the acute cases ranges from an erythema resembling sunburn to a severe vesicular or bulbous inflammation with exudation, bleeding and ulceration with secondary infection In chronic cases there is more roughness scaling thickening and crusting or cracking, with a brownish pigmentation In cases in which the lesions are healed the skin may be thin and atrophic In the chronic cases sites of predilection are the dorsa of the hands, elbows, ankles knees and neck

The tongue and buccal mucosa in acute cases are bright red and swollen, often with ulceration and secondary infection The papillae of the tongue are atrophic in varying degree the tongue often being 'bald and glazed in the more severe cases of longer duration Often the tongue is dry, but there may be increased salivation The pharynx and esophagus may be similarly involved and chewing and swallowing may be difficult or impossible With the involvement of the intestine there is usually diarrhea even in chronic cases which may vary from several loose stools a day to severe often bloody, watery diarrhea with mucus and tenesmus There is often severe proctitis and in women vaginitis

The mental symptoms range from changes in disposition irritability depression poor concentration apathy and poor memory to acute delirium The latter is of the so called toxic infectious type In the more severe chronic cases there may be an actual dementia but confusion, loss of memory and depression are more common Such neurologic manifestations as degeneration of posterolateral tract with ataxia spasticity and involvement of the sphincters may be a part of pellagra The nervous manifestations are more frequent in the older subjects In acute severe pellagra there may be fever and other constitutional symptoms Other changes often seen in pellagra are more likely the result of other deficiencies than that of niacin

themselves but because without them one is *not likely* to use supporting laboratory evidence or the highly *important therapeutic test*

The laboratory tests of niacin deficiency are not particularly good or readily applicable Yet, like some of the other laboratory tests for vitamin deficiencies they do have a definite value The most reliable and useful tests in common use are measurements of the excretion of niacin and substances resulting from the breakdown of niacin in the body either spontaneously or after the administration of a test dose of niacin or niacinamide Only a relatively small portion of niacin is excreted as such and the excretion shows little variation with different levels of intake, even in pellagra *There is also considerable variation in* the excretion of N methylniacinamide which is one of the larger fractions but accounts for only 20 to 30 per cent of a test dose of niacinamide Nevertheless the measurement of the excretion of this substance for one hour with the patient in a fasting state or for longer periods or after the administration of a test dose *can yield helpful information*[57]

Like all similar tests those for the excretion of niacin suffer from lack of standardization and the failure to accumulate a large clinical reference by concentration on a single technic Even less uniformity exists in regard to standards than exists with the excretion tests of other vitamins Johnson[58] has suggested *an excretion of* 0 03 mg or less of *N methylniacinamide* in one hour while the patient is fasting as indicating smaller tissue stores than normal and less than 0 5 mg in four hours after administration of 50 mg of niacinamide by mouth as indicating chemical deficiency *Despite the drawbacks conservative interpretation* and the use of values at or near the zero level make the test useful

Incidence—The incidence of pellagra and presumably the less severe deficiencies of niacin has declined

57 Ruffin J M Cayer D and Perlzweig W A The Relation Between the Clinical Picture of a Mild or Early Vitamin Deficiency and Laboratory Determinations of Vitamin Levels Gastroenterology 3 340 1944 Sargent F Robinson P F and Johnson R E F and F_2 of Najjar and Holt in Urine of Normal Young Men J Clin Investigation 23 714 1944 Najjar V A and Holt L E Jr Excretion of Specific Fluorescent Substances in Urine in Pellagra, Science 93 20 1941

58 Johnson R E Sargent, F Robinson P F and Consolazio F C. Assessment of Nutritional and Metabolic Condition in the Field General and Clinical Aspects War Med. 7 227 1945

cially on the backs of the hands, seem to be more the effect of a chronic deficiency following severe, acute pellagra

The nervous and mental symptoms seem to be relatively more common and more of a feature in the mild and especially the chronic cases They are apt to be more confusing in respect to diagnosis and recognition of their true significance often escapes one particularly in the absence of dermatologic, mucous membrane and gastrointestinal symptoms which is not infrequent. The manifestations are not specific They consist of irritability decreased powers of attention and concentration, lack of interest, personality changes and perhaps some memory disturbances With this there may be some confusion loss of judgment and actual decrease in mental ability How much this may be due to associated deficiencies that of thiamine for example, may be doubtful, but I am of the opinion that much perhaps all, of it can result from niacin deficiency alone because of the response and relief of these symptoms after treatment with niacin alone

Diagnosis—The diagnosis of pellagra is ordinarily easily made on the basis of symptoms and physical changes alone if one only keeps the disease in mind The combination of glossitis gastrointestinal symptoms and a symmetric dermatitis can scarcely be misinterpreted Efforts to obtain a reliable diagnosis of earlier and milder lesions as well as finer differentiation in respect to duration (chronicity) and severity by means of microscopic examination of the tongue have, unfortunately been unsuccessful [56] Occasionally severe mental disturbance in the absence of or in association with only mild lesions and symptoms elsewhere will be misleading and missed unless one bears the possibility in mind The key to such a situation should be the history or knowledge of a possible deficiency or inadequate food intake

For the mild or early severe deficiencies the key to diagnosis is again the symptoms and physical signs, supported by or detected because of knowledge of the dietary defect In this instance however the signs and symptoms are the key not because they are sufficient of

56 Kruse H D The Lingual Manifestations of Anacinosis with Especial Consideration of the Detection of Early Changes by Biomicroscopy Milbank Memorial Quarterly 20 62 1942 Lesions of the Tongue and Niacin Deficiency Nutrition Rev 6 189 1948

usually be reduced in a few days, and often administration of the vitamin can be discontinued in a week or ten days and replaced by concentrates and correct diet

In some cases particularly in severe, acute cases in which there is extensive glossitis and stomatitis in cases in which there is mental disturbance and in cases in which there is other, interfering disease, it may be necessary to administer the vitamin parenterally Sometimes this can be done with a stomach tube but the nature of the lesions less often permits this procedure The vitamin can be given intravenously or intramuscularly in concentrations of 0 10 to 1 per cent in isotonic sodium chloride solution The intravenous route is preferable Other nutrients or drugs can be incorporated Ten to twenty milligrams or even larger amounts can be given especially in the high dilutions and when given slowly For the reasons stated previously, use of the amide (niacinamide) is preferred If the acid is used, vasomotor reactions must be watched and the frequency of dosage limited Liver extracts (crude) are also useful and may be employed parenterally in the acute phases Ordinarily parenteral treatment may be stopped after a few days and treatment continued by mouth The doses for children are smaller 10 mg by mouth being sufficient for infants and young children and 25 mg for adolescents with the total dose per day in proportion

Other nutrients should be administered as indicated, and the diet should be as liberal and general as possible These patients are usually greatly undernourished and require a high caloric and protein intake until weight has been regained Whenever possible the cause—ignorance economic status alcoholism or other disease—should be removed, but some patients will require maintenance doses of the vitamin or concentrates because of the nature of their other illnesses Apparently in some persons with chronic pellagra changes occur which interfere with absorption or utilization These persons require larger intakes, which are even then not always completely effective

The local lesions such as the dermatitis and stomatitis often do not require any special treatment, but treatment of secondary infection may be necessary Wet sodium chloride dressings and a protective cover-

phenomenally in this country in the last ten years Word of mouth reports from regions where pellagra was *formerly* common indicate its virtual disappearance and such informal evidence is well supported by the study of Bean Vilter and Blankenhorn [59] In a hospital where pellagra had been relatively common only 1 case had been observed in thirty months prior to the time of writing of this report There is undoubtedly a small residue of cases of pellagra, largely confined to patients with such illnesses as cancer of the esophagus and stomach, alcoholism and insanity which produce conditions responsible for the disease There is no way to estimate the frequency of pellagra sine pellagra or mild deficiency of niacin In 1941 only about 16 per cent of a population in a region in which pellagra had been endemic had symptoms and signs which might possibly have been pellagrous [48] Elsewhere in the world where conditions favoring nutrition are less good pellagra still flourishes

Treatment —Aside from prevention and the treatment of patients with mild cases with a liberal anti pellagra diet *treatment of the primary deficiency* rests mainly on the use of niacin, or better, the amide (niacinamide) The flushing reaction to the acid is avoided by the use of the amide which is almost exclusively employed at present unless the flushing reaction is specifically wanted for other reasons Concentrates such as yeast and liver extracts can be used in the milder cases and are always indicated as supplements to the diet or to treatment with the pure chemical but even in mild cases with definite lesions it is better that niacin or amide be given initially in order to secure prompt and decided results Ordinarily they can be given by mouth The response is prompt and often dramatic Often the diarrhea stops within twenty four hours the mental confusion clears and the tongue and mouth become nearly free of soreness The dose varies with the severity of the symptoms Severe mental symptoms and diarrhea usually indicate need for larger doses In cases of moderate severity 50 to 200 mg of the acid or amide daily in divided doses will usually suffice Even in severe cases it is seldom necessary to give more than 500 mg Such doses can

59 Bean W B Vilter R W and Blankenhorn M A Incidence of Pellagra, J A M A 140 872 1949

clinical point of view, in the blood plasma and in the leukocytes and a diminished excretion of the vitamin in the urine. No attempt will be made at this point to discuss the relation of decreased concentration in the blood or tissues or diminished excretion to the existence of a state of disease.

The primary structural change in vitamin C deficiency is a disturbance in the formation and maintenance of the intercellular ground substance. Apparently ascorbic acid is essential for the integrity of this tissue. In the intercellular ground substance are the collagen bundles. In the absence of a sufficient supply of ascorbic acid, the collagen bundles disappear and the ground substance takes on a thin "watery" appearance and may eventually disappear. If ground substance is laid down, it is imperfect, collagen bundles and fibers are scarce or lacking. If the deficiency is severe, no ground substance is formed. Conversely, when adequate amounts of ascorbic acid are supplied, normal collagen and ground substances are laid down. Inasmuch as this ground substance is the essential matrix of connective tissue, the defect, simply expressed, is a lack of proper connective tissue, and since connective tissue constitutes the effective framework tissue of all organs and structures, a defect in this tissue will explain the multiple, widespread and varied lesions of scurvy. The defect in the so-called cement substance of the capillaries, a lesion responsible for the various hemorrhagic manifestations, can be considered in the same category.

In the mildest cases the changes are slight or lacking; when they are more severe they constitute the characteristic pathologic changes of scurvy. These in turn vary in severity. The most striking structural changes, both gross and microscopic, occur in the bones of children. As in other conditions, the deficiency is apt to affect most severely young, rapidly growing tissue. One such tissue in the child, especially in the infant, is the skeleton.

The earliest microscopic change is an alteration in the osteoblasts, which become deformed, leave the trabeculae, come to resemble fibroblasts and even produce collagen and fibrils.[61] The orderly arrangement of the columns of cells in the proliferative cartilage and

61 Eddy, W. H., and Dalldorf, G.: The Avitaminoses: The Chemical, Clinical and Pathological Aspects of Vitamin Deficiency Diseases, ed. 3, Baltimore, The Williams & Wilkins Company, 1944.

ing may give some relief early but are not needed long Sedatives and restraint may be required during acute stages

VITAMIN C

The fully developed result of vitamin C deficiency is scurvy, lesser grades of the deficiency result in varying degrees of change in the tissues and organs affected in scurvy and in the mildest discernible cases, in biochemical evidence of a deficient tissue content of ascorbic acid, with or without symptoms which may be related to that deficiency

The chemical characteristics of ascorbic acid and its role in oxidative and reduction processes are well known and have been described elsewhere[1] As will be discussed, the organic changes and some of the abnormal biochemical mechanisms resulting from a deficiency of ascorbic acid are readily demonstrated if the deficiency is great enough Yet the exact mechanism by which the altered biochemical mechanism causes the organic changes remains unknown

The most striking biochemical lesion observed clinically occurs in infants Ascorbic acid is essential for the proper metabolism of the amino acids, tyrosine and phenylalanine, and, in premature infants and in normal infants given large amounts of such amino acids, the excretion of abnormal metabolic products of the breakdown of these amino acids can be demonstrated in the urine[60] This occurrence can be abolished by treatment with ascorbic acid A specific symptom or physical effect of this abnormality is not apparent, though it might be supposed to have an effect on growth because of interference with normal protein metabolism it may of course be related to the various pathologic processes which appear as scurvy in the more severe deficiencies

The other physiologic abnormalities associated with vitamin C deficiency are a decrease in the concentration of ascorbic acid in the tissues, particularly from the

60 Sealock R R and Silberstein H E The Excretion of Homogentisic Acid and Other Tyrosine Metabolites by the Vitamin C Deficient Guinea Pig J Biol Chem **135** 251 1940 Levine S Z Gordon H H and Marples E A Defect in the Metabolism of Tyrosine and Phenylalanine in Premature Infants II Spontaneous Occurrence and Eradication by Vitamin C J Clin Investigation **20** 09 1941 Sealock R R Perkinson J D Jr and Babinski D H Further Analysis of the Role of Ascorbic Acid in Phenylalanine and Tyrosine Metabolism J Biol Chem **140** 151 1941 Babinski D H and Sealock R R Structural Specificity of Tyrosine in Relation to the Metabolic Action of Ascorbic Acid J Biol. Chem **166**:7 1946 Fishberg E H Excretion of Benzoquinoneacetic Acid in Hypovitaminosis C J Biol Chem **173**:15 1948

Resolution of the changes is rapid with adequate treatment, histologic evidence of repair appearing within a few hours after treatment with vitamin C is started Fibroblasts begin to form new connective tissue, and capillary buds invade the area of hemorrhage In the bone a line of calcification appears suddenly throughout the length of the periosteum incidentally furnishing a helpful confirmation of diagnosis and sometimes an initial diagnostic sign The periosteum contracts down to the shaft normal bone formation is resumed almost at once, new trabeculae form and eventually the deformities disappear

In adults the skeletal lesions are much less frequent and extensive and obviously have no counterpart to the epiphysial lesions of childhood Subperiosteal hemorrhage is the more frequent of such lesions

The lesions of the capillaries cause hemorrhage in many parts of the body those in the skin being frequent, most apparent and hence most useful in diagnosis The most characteristic lesion is a perifollicular petechial hemorrhage often with hyperkeratosis about the follicle which may or may not be due to the deficiency of vitamin C (It does not always accompany the hemorrhage)

There may be purpuric or ecchymotic hemorrhages even suggillations Subcutaneous or intramuscular hemorrhages (hematomas) may develop often extending along fascial planes Such hemorrhages as do those of the skin occur in areas of stress and strain and are more common in the lower extremities In infants hemorrhages in the skin are less common but tend to occur in areas of stress such as at the border of the diapers There may be hemorrhages into the orbit or various structures of the eye into the serous cavities or less commonly, into parenchymatous organs Epistaxis is common and the blood often appears thin' and brownish the result of anemia

Edema occurs usually confined to the lower extremities although the patient may have a generally bloated pale appearance The edema is presumably due to increased permeability of the capillaries though it may be complicated by edema of other origin, including that of cardiac weakness There may be pericardial peritoneal and pleural effusions hemorrhagic or non hemorrhagic.

the function of the cartilage shaft is disturbed and the normal "lattice" of calcified cartilage is replaced by irregular masses of calcified cartilage in fibrous tissue This causes widening and irregularity of the lattice, which appears brittle, with microscopic fractures leading to the displacement of fragments

With this, the atypical osteoblasts fail to form new bone and new trabeculae This leads to development of a zone of rarefaction, a zone free of trabeculae between the older previously formed trabeculae and the calcified matrix This rarefied zone is essentially fibrous and a zone through which "subepiphysial infractions," or 'epiphysial separation," occurs At the same time bone formation ceases and bone resorption continues, perhaps is even accelerated, so that a general thinning of the whole bone occurs, particularly next to the cartilage

The normal marrow is replaced at the epiphysial end by so called frame-work' marrow and loose connective tissue containing few cells and much abnormal intercellular ground substance resembling embryonic connective tissue This tissue forms a band across the epiphysial end of the bone and joins with the zone of rarefaction to form the zone of the 'Trummerfeld and the 'Gerüstmark' shown in roentgenograms The periosteum is loose and easily raised even without underlying hemorrhage, which however is common and may strip the periosteum except for its attachments to the perichondrium The centers of ossification in flat bones undergo similar changes but to a lesser degree and with modifications resulting from the structural differences

As indicated many of these changes can be recognized in the roentgenogram before they are apparent on physical examination The gross changes which can be recognized on physical examination as well as in the roentgenogram consist of a widening of the ends of the long bones (and of the costochondral junctions) resembling a similar widening seen in rickets The areas most commonly affected clinically are the distal end of the femur the proximal end of the tibia and humerus and the costochondral junctions Both the microscopic and gross changes although characteristic may be confused with those of rickets and may be difficult to detect when the latter disease complicates the scurvy, as is not uncommon

of such a nature and that some of the first named kind but fewer have, as either a primary or a contributing cause a deficiency of vitamin C However this is difficult to determine in a given person by inspection alone and without the use of accessory diagnostic aids especially a controlled therapeutic test Nor is the situation helped by the view that cases of chronic gingivitis which do not respond to months of adequate treatment with vitamin C fail to do so because the treatment has not been continued long enough One characteristic of a nutritional deficiency disease is that it responds promptly to specific treatment unless irreversible changes have occurred These changes are in effect scars and it is possible that a certain portion of the changes in chronic gingivitis are of such a nature as are the muscle atrophy remaining after a severe attack of beriberi or the scars of the cornea after an attack of xerophthalmia (keratomalacia)

In scurvy no correlation has been found between the incidence of gingivitis and other evidence of vitamin C nutrition or undernutrition A positive correlation with advancing age has been apparent in some studies [65]

Definite and characteristic changes occur in the teeth Resorption of the dentin begins along Tomes canals the dentin being replaced by osteodentin an inferior material This resembles the changes which occur in the bones The cementum is similarly affected Hyperemia and edema of the pulp is followed by atrophy and degeneration of the odontoblast layer Hemorrhage into the pulp with the formation of cysts and areas of calcification or actual osteoid tissue may occur The teeth may loosen as a result of rarefaction of the alveolar processes Similar changes probably occur in children and there is little doubt that normal dentition is disturbed with resultant defective formation Because scurvy in children is most common in infants under 2 years of age the effects on the teeth are only apparent later Similarly scurvy later in childhood is apt to affect most the nonerupted teeth which are the more susceptible structures The relation of vitamin C to caries if any is undetermined

65 Youmans J B Patton, E. W Sutton W R. Kern R. and Steenkamp R. Surveys of Nutrition of Population Vitamin C Nutrition of a Rural Population in Middle Tennessee J Hygiene 42 254 1945

The gums unquestionably are one of the sites of the most common, earliest and most easily observed lesions in scurvy [6] and these lesions are one of the traditional and classic signs and symptoms of the disease The gingivitis begins with hyperemia and redness of the interdental papillae, followed by swelling, hemorrhage, ulceration and secondary infection In some cases the gums become so swollen and hypertrophied that they cover the teeth, even the cusps, and are bitten with each bite or chew with resultant bleeding Bleeding in general may follow mild trauma or be spontaneous The secondary infection often including that caused by spirochetal invaders and Borrelia vincenti, may lead to extensive sloughing With severe scurvy the teeth become loosened and may be easily pulled with the fingers or lost spontaneously From a bright red the color of the gums changes to a dusky livid hue

While it is certain that vitamin C deficiency of a sufficient degree (scurvy) causes gingivitis it is not at all clear that all gingivitis or even any great portion of it, as commonly observed in surveys or in practice, is the result of vitamin C deficiency [63] There is as Kruse has pointed out [64] a variation in intensity and in duration of the deficiency as in all nutritional deficiency disease which makes it possible to speak of mild acute severe acute mild chronic or severe chronic gingivitis There can even be the superimposition of an acute on a chronic process It does not follow however that all cases of gingivitis with thickened blunted contracted and fibrous papillae and margins are caused by chronic vitamin C deficiency nor that all persons with slightly swollen shiny, slightly reddened interdental papillae have mild acute gingivitis due to vitamin C deficiency It is my opinion that many cases of the latter especially in children and young persons with good dentures are

62 (*a*) Campbell H G and Cook R P Treatm nt of Gingivitis with Ascorbic Acid Br t M J **1** 360 1941 Burrill D Y Relat onship of Blood Pla ma Vitamin C Lev l to Ging val and Period ntal D sease J Dent Research **21** 353 1942 Stamm W P Macrae T F, and Yudkin S Inc dence of Bleed ng Cums Am ng R A F Personnel and the Value of Ascorb c Acid in Treatment Brit M J **2** 239 1944 (*b*) Leeson H J and other Study of A corbic Ac d Nutr tion Canad M A J **53** 341 1945 (*c*) Linghome W J McIntosh W G Tice, J W Tisdall F F McCreary J F Drake T S Greaves A V and Johnstone W M The Relat on of Asco bic Acid to G ngivitis Canad M A J **54** 106 1946

63 Darby W J and M lam D F Field Study of the P evalence of Clin cal Manifestations of D etary Inadequacy Am J Pub Health **35**: 1014 1945 Footnot 62

64 Krus H D A Concept of the Deficiency States M lbank Memorial Fund Quarterly **20** 245 1942

In addition to the biochemical and structural evidences of vitamin C deficiency, there are a few constitutional symptoms which though not specific, are common and characteristic By far the most important of these is pain which in children is the most frequent manifestation and often the only one This pain most often arises from the long bones and may be sufficiently severe to cause immobility and lead to a mistaken diagnosis of paralysis With the pain there is local tenderness Children especially infants fail to grow and gain weight (except for edema) and are pale, weak and irritable Fever, rapid and shallow breathing (costochondral involvement) a rapid pulse and, sometimes vomiting and diarrhea may develop Adults usually have pain in the joints weakness and lassitude Palpitation and shortness of breath accompany the more severe deficiencies

Diagnosis—In addition to the history, which may reveal a dietary deficiency the symptoms which are usually vague and the physical signs which are often lacking except in actual scurvy the diagnosis of ascorbic acid deficiency depends on certain special procedures and laboratory tests Actually as in most diseases, the diagnosis is the result of an accumulation of evidence from several of these sources

One of the special diagnostic procedures is the roentgen examination of the skeleton or parts of it The signs detected by roentgen examination have essentially the same defects and virtues as the other physical signs They are characteristic When clearly present they may be the first as well as the conclusive signs in infants because of the peculiar circumstances which often lead to a delayed diagnosis in these patients Actually the diagnosis in such cases is often suspected, despite the absence of other signs and therefore the roentgen examination is made In mild cases however and in older children and adults the roentgenographic appearance of the condition unless it is a surprise observation is present only a little ahead if any, of other signs It is helpful in a confirmatory way and as a check on improvement (calcification of subperiosteal hemorrhages during and following treatment) The roentgen signs are not specific and may be obscured by rickets when the latter is present but taken as a whole and in the light of other findings, they

In addition to the well known pathologic changes just described, severe and chronic scurvy may produce degenerative changes in the skeletal muscles cardiac hypertrophy, atrophy of the bone marrow with anemia[66] and atrophy of the adrenals In addition to the possible direct relation between such changes and the body stores of vitamin C (the adrenals, for example, are especially rich in vitamin C), secondary causes are probably responsible for a part of these changes For example, anemia, edema and increased capillary permeability, that is, poor nutrition and overwork probably account for much of the cardiac enlargement

In the mild deficiency of vitamin C, none of the lesions previously described are apparent, with the possible exception of the gingivitis This means that they are rarely seen because there is little actual scurvy seen at least in this country and the vast majority of patients with vitamin C deficiency will not exhibit them There are microscopic lesions before gross lesions appear, but there is usually little reason to suspect them When they are suspected, it is difficult or impractical to demonstrate them with one or two exceptions One of these is the increased capillary fragility, which may be made apparent by the capillary resistance test It is interesting to note, however, that certain unintentional circumstances may disclose the presence of a deficiency under conditions of clinical significance One of these is the healing of wounds which may be impaired in the presence of unsuspected vitamin C deficiency[67] The other is the occurrence of certain infectious diseases accompanied by exanthems which in the presence of vitamin C deficiency may be hemorrhagic Finally it should be pointed out that some of the biochemical lesions may be disclosed by special procedures which can be used as diagnostic tests

66 (a) Vilter R W Woolford R. M and Spies, T D Severe Scurvy A Clinical and Hematologic Study J Lab & Clin Med 31 609 1946 (b) Vilter R W Symposium on Nutrition of the Robert Gould Research Foundation edited by Arthur Lejwa, Cincinnati Robert Gould Research Foundation Inc 1 179 1947

67 Lanman T H and Ingalls T H Vitamin C Deficiency and Wound Healing An Experimental and Clinical Study Ann. Surg 105 616 1937 Carney H M Wound Healing with Low Vitamin C Level, Ann Surg 123 1111 1946. Bartlett M K Jones C M and Ryan, A. E Vitamin C Studies on Surgical Patients, Ann. Surg 111 1 1940

dyscrasias but in some without apparent cause Hence, it is not usually considered reliable It may be used however, as a screen A negative result of the test would be evidence against the deficiency, while a positive result would be suggestive of it and an indication for other tests

The biochemical tests of tissue concentration and storage, despite some of the deficiencies they possess are the most reliable and useful procedures available for the diagnosis of mild ascorbic acid deficiency, that is, deficiency below the level of scurvy Undoubtedly, the most useful of these is the determination of the concentration of vitamin C in the blood plasma (serum) The values obtained have little significance in ordinary practice or use except at a level of concentration of zero or near zero As Lowry and his associates have shown[70] when the levels of ascorbic acid fall below 0.3 mg per hundred milliliters of plasma, the concentration of ascorbic acid in the leukocytes has begun to drop Symptoms do not ordinarily begin to appear until the concentration in the leukocytes and platelets has dropped to a low level When the levels of ascorbic acid in the plasma reach zero or near zero (*even with scurvy some vitamin C is often found in the* serum values of 0 05 to 0 1 mg per hundred milliliters being frequent and zero concentration often *lacking*) *the concentration in the leukocytes may for* practical purposes be considered to be seriously reduced and this reduction may be taken to indicate the first *stage of actual deficiency* (disease) *which* can be readily recognized (Occasionally cases are encountered in which there are extremely low values without signs *of scurvy* and *conversely in rare cases in which* there are extremely low values and signs of scurvy there is no rise in concentration despite administration of large doses of the vitamin) *As is well known* a decrease in the concentration of ascorbic acid in the leukocytes accompanies or shortly precedes, the occurrence of gross signs of scurvy[71] Values *above zero* in the

70 Lowry O H Bessey O A Brock M J and *Lopez*, J A The Interrelationship of Dietary Serum White Blood Cell and Total Body Ascorbic Acid J B l Chem. **166** 111 1946

71 Crandon J H Lund C C *and Dill D B* Experimental Human Scurvy New England J Med **223** 353 1940 Vitamin C Requirement of Human Adults Experimental Study of Vitamin C Deprivation in Man *A Preliminary* Report by the Vitamin C Subcommittee of the Accessory Food Factors Committee Medical Research Council, Lancet **1** 853 1948

are characteristic[68] In early cases it is difficult to decide whether or not they actually are present The signs are as follows (*a*) Deformity of soft parts from edema or hemorrhage This may be subcutaneous muscular or subperiosteal (*b*) So called ground glass atrophy, especially at the end of the shaft of the bones (*c*) *Cortical atrophy*, with apparent increase in the width of the marrow cavity (*d*) Increased density and widening of the zone of preparatory calcification, the "white line" of Frankel, at the epiphysial ends of the long bones (*e*) Similar changes in correspond *ing areas in epiphysial centers of ossification* (*f*) The zone of rarefaction ('Gerustmark") in the shaft next to the zone of provisional calcification (*g*) Similar changes in the interior of centers of ossification, with loss of trabecular markings Simple atrophy *leaves these markings* (*h*) *So-called epiphysial* sepa ration, often displaced toward the shaft or laterally Separation occurs through the zone of rarefaction (*i*) The presence of lateral spurs near the epiphysial junction resulting from the displacement of the epiphy sis or calcification of the periosteum (*j*) Calcification (ossification) of the elevated periosteum This is a sign of healing (*k*) Subperiosteal, comminuted frac tures of the cortex

Another special procedure is the capillary resistance test This is a test designed to disclose through the mechanism of mechanical stress a defect in the capillary wall not yet manifest spontaneously A number of technics have been devised[69] The original method con sists of the obstruction of the venous return in the arm which raises the venous and hence the capillary pressure and causes hemorrhages in those subjects *with the* capillary defect Negative pressure (cupping) also has been used Unfortunately although the result of the test is positive in deficiency of sufficient degree it is also positive in many persons who have no deficiency *of vitamin* C not *only in* those with certain blood

68 Kato K Critique of the Roentgen Signs of Infantile Scurvy with Report of 13 Cases Radiology **18** 1096 1932 Park E A. Guild H G Jackson, D and Bond M Recognition of Scurvy with Especial Reference to Early X Ray Changes Arch Dis Childhood **10** 265 1935 Bromer R S Roentgen Ray Diagnosis of Infantile Scurvy Am. J Roentgenol **19** 112 1928 **49** 5 5 1943

69 Gothlin G F Outline of a Method for the Determination of Strength of *Skin Capillaries* and the *Indirect Estimation* of the *Indi* vidual Vitamin C Standard J Lab & Clin Med **18**:484 1933 Dalldorf G A Sensitive Test for Subclinical Scurvy in Man Am J Dis Child. **46** 794 (Oct) 1933

dyscrasias but in some without apparent cause Hence it is not usually considered reliable It may be used, however, as a screen A negative result of the test would be evidence against the deficiency while a positive result would be suggestive of it and an indication for other tests

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70 Lowry O H Bessey O A Brock M J and Lopez, J A. The Interrelationship of Dietary Serum White Blood Cell, and Total Body Ascorbic Acid J Biol. Chem. 166 111 1946

71 Crandon J H Lund C. C and Dill D B Experimental Human Scurvy New England J Med. 223 353 1940 Vitamin C Requirement of Human Adults Experimental Study of Vitamin C Deprivation in Man A Preliminary Report by the Vitamin C Subcommittee of the Accessory Food Factors Committee Medical Research Council, Lancet 1 853 1948

plasma vary over a wide range without apparent significance in respect to truly pathologic decreases in the leukocytes or tissues It must be realized of course that zero concentration in the plasma does not indicate how much lower the leukocyte or tissue content may be nor how long such a deficiency may have existed Hence, a concentration of zero may exist with or without the presence of manifest scurvy Also, temporary decreases in concentration, unrelated to a deficiency in the tissues, occur from such causes as infections The determination of the concentration of ascorbic acid in the leukocytes can be made and gives additional information of value but is more difficult than measurement of the concentration in the plasma. Both macromethods and micromethods are available for the determination of the concentration of ascorbic acid in the plasma or serum[72] and in the white layer (leukocytes and platelets)[73]

Measurement of the excretion of the vitamin in the urine, with or without a "load test is useful and technically is simpler than an analysis of the blood There are several technics which are suitable for clinical use[74] They are less often used, however, than analyses of the blood because of the trouble of collecting and preserving properly a twenty-four hour urine specimen Also the test has been subject to criticism (as has the determination of the ascorbic acid in the blood) on the basis of the effect of the immediate diet This effect however, has been exaggerated as far as practical use is concerned Although a decrease in excretion does

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72 Farmer C J and Abt A F Determination of Ascorbic Acid in Small Amounts of Blood Proc Soc Exper Biol & Med **31**:146 1936 Bessey O A A Method for the Determination of Small Quantities of Ascorbic Acid and Dehydroascorbic Acid in Turbid and Colored Solutions in the Presence of Other Reducing Substances J Biol Chem **126** 771 1938 Mindlin R L and Butler A M Determination of Ascorbic Acid in Plasma Macromethod and Micromethod J Biol Chem **122**: 673 1937 1938 Lowry O H Lopez J A and Bessey, O A Determination of Ascorbic Acid in Small Amounts of Blood Serum, J Biol Chem **160** 609 1945

73 Butler A M and Cushman M Distribution of Ascorbic Acid in Blood and Its Nutritional Significance J Clin Investigation **19** 459 1940 Lubschez R Studies in Ascorbic Acid with Especial Reference to White Layer Description of Method and Comparison of Ascorbic Acid Levels in Whole Blood Plasma Red Cells and White Layer J Clin Investigation **24**: 573 1945 Bessey O A Lowry O H and Brock, M J Quantitative Determination of Ascorbic Acid in Small Amounts of White Blood Cells and Platelets J Biol. Chem. **168** 197 1947

74 Abbasy M A Harris L J Ray S N and Marrack J R Diagnosis of Vitamin C Subnutrition by Urine Analysis Quantitative Data—Experiments on Control Subjects Lancet **2** 1399 1935 Evelyn K A Malloy H T and Rosen C The Determination of Ascorbic Acid in Urine with the Photoelectric Colorimeter J Biol Chem **126** 645 1938.

occur quite promptly after dietary restriction, it does not reach minimum levels (around zero) in a person whose diet has in general been reasonably adequate Such a low excretion indicates that the diet has been deficient for some time and hence that a deficiency may exist When such an observation is combined with the failure of the excretion to rise significantly after the administration of an adequate test dose, a low tissue concentration may be assumed and with it the possibility of an actual pathologic deficiency state Many methods, varying in dosage, time and other conditions, have been used but no one has been adopted generally as standard[75] An excretion of less than 3 mg in four hours after administration of a test dose of 500 mg of ascorbic acid has been suggested by Johnson as evidence of a chemical deficiency[76] Such tests provide a roughly quantitative measure of the tissue content (by the repetition of test doses until the level of excretion rises) Obviously a zero excretion and a zero or near zero response to load tests may occur with or without other signs of a deficiency (scurvy)

Tests of the concentration of ascorbic acid in the blood and of the urinary excretion as diagnostic aids have been severely criticized and declared of little or no value This has been the result of an attempt to read more into the tests than was justified Most often the criticism has been based on the failure to establish a positive correlation between the results of such determinations and such factors as dietary intake and non specific inconstant inconsistent and sometimes nonsignificant physical signs and symptoms Such correlation should not be expected except at the extremes of a very wide range In particular no such correlation should be expected at concentrations of vitamin C in the blood above zero or at levels of excretion above insignificant amounts

Unfortunately in practice the physician tends to depend too greatly on the therapeutic trial or test This procedure which is a valuable tool is too often used in an uncritical fashion

Incidence—The incidence of the actual state of pathologic vitamin C deficiency is difficult to determine

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75 Youman, J B and Patton, E W The *Laboratory Diagnosis of Nutritional Deficiencies* Clinics 1:303, 1942

76 Johnson R E, Sargent F Robinson P F and Consolazio, F C Assessment of Nutritional and Metabolic Condition in the Field General and Clinical Aspects, War Med. 7:2?7 1945

A distinction must be made between an apparently deficient intake of the vitamin or a diminished concentration in the tissues and an actual pathologic state either structural or functional

Scurvy is easy to recognize In this country it is probably *most frequent in children A fairly accurate* idea of its frequency can be gotten from such studies as those of Vilter and his associates[66a] and Dogramaci[77] but the frequency of hypovitaminosis C a pathologic state of ascorbic acid deficiency less severe than scurvy is a different matter Most modern estimates of the incidence have been made on the basis of the dietary intake, the physical signs of the disease notably gingivitis, and the *concentration of the vitamin in the tissues* as reflected by its concentration in the blood The difficulty with the interpretation of these data is that relatively few studies, on relatively few subjects, have been made of the correlation of the tissue (structural) and physiologic (functional) lesions and the intake and concentration of vitamin C in the tissues To put it more simply there have been relatively few simultaneous studies of intake concentration in blood and tissues and biopsies (bone connective tissue and capillaries) and still fewer studies of a longitudinal character *following with these technics the development of* the state of deficiency from the start of deficient intake to the appearance of scurvy The few such studies that have been made have demonstrated a great lag in the appearance of detectable signs of the disease in relation to deficient intake and decline in tissue stores and a failure of the former to parallel to a close degree changes in the latter There is likewise a failure to demonstrate a successive appearance of signs indicating a progressively more severe deficiency For instance changes in the gums often considered an early sign or in certain grades one of *slight deficiency need not* appear in experimental scurvy until other obvious signs are present[8] It must be remembered however, that in experimental scurvy *the subjects have usually been* healthy young adults with a single deficiency, who have not been subjected to the stresses and strains including infections physical exertion and environ

77 Dogramaci I Scurvy A S rvey of 241 C ses N w England J Med 23. 185, 1946 McMill n R. B and Inglis J C Scurvy A Survey of *53 Cases Brit. M J 2 233 1944*

78 Ascorbic Acid and the Health of the Gums Nutrition Rev 3: 44 1945 Crandon Lund and Dill[1]

mental stress which occur under natural conditions and which may well modify the picture of the disease Furthermore, in experimental scurvy a long period of depletion has been necessary while in a general population there may be many whose stores have become depleted and who are in a precarious balance and are dependent on the day s supply These facts must be considered in interpreting the significance of the period of deficient intake, as must recent evidence indicating that requirements may be much smaller than has often been assumed

Perhaps the soundest approximation of the frequency of hypovitaminosis C can be gotten from surveys in which determinations of the concentration of ascorbic acid in the blood have been made provided that the findings are interpreted in the light of conclusions drawn from such studies as those of Lowry and his associates [70] According to this one might assume with some justification that values of zero or near zero represented a pathologic state of deficiency on the basis that at this concentration in the plasma, the concentration in the leukocytes had reached or was about to reach a concentration accompanying or presaging imminent scurvy It is not necessary indeed it is incorrect, to assume that a pathologic state does not exist unless there is actual scurvy

It should be remembered however that temporary depression of the concentration of ascorbic acid in the blood can occur without indicating a deficiency in the tissues (as may result from infections) and that in any subject the interpretation of the findings must be made in the light of all the evidence On this basis, hypovitaminosis C can be assumed to exist in from 7 to 50 per cent of such groups as a general population [65] and the inmates of a mental hospital [8 b] respectively

Treatment—In mild cases vitamin C deficiency can be satisfactorily treated with natural foods having a high vitamin C content such as citrus fruit juices Even patients with moderately severe deficiencies such as those in whom there are early signs of actual scurvy can be relieved fairly quickly by similar means though it is usually advisable to use pure chemical preparations in the initial treatment of such patients Deficits of ascorbic acid in such cases usually amount to 2 or 3 Gm, and it is easier to supply such amounts in a

concentrated form, particularly as the sore mouth in such cases may interfere to some extent with ingestion The latter condition may make it necessary to give the vitamin parenterally, however, this is unusual Intra venous administration is to be preferred to intra muscular For intravenous injection it is not necessary that the acid be neutralized, if doses of only a few hundred milligrams, well diluted, are given slowly A 10 per cent solution is satisfactory Large doses should be neutralized, as should solution for intra muscular use When neutralized it should be used at once, because it is destroyed rapidly under these conditions Total doses of 300 mg of ascorbic acid a day will suffice in most cases of mild to moderate scurvy, and less will be adequate in latent or slight deficiencies

It is useful to determine the deficit and the relief of the deficit by means of tests of the excretion of the vitamin in the urine especially in doubtful cases A proper diet and dietary intake is of great importance particularly in the correction of previous errors and the prevention of recurrences

No specific toxic effects result from even relatively enormous doses of the vitamin Reference has been made to the possibility of harm from the acid reaction of the solutions of the pure chemical There may be rare instances of allergic sensitivity to foods rich in vitamin C and perhaps an idiosyncrasy to ascorbic acid itself

Ordinarily all the manifestations of scurvy respond promptly to administration of an adequate supply of the vitamin and no other treatment is needed Occasionally local treatment of ulcerative lesions is required but simple cleanliness is about all that is required The application of strong solution is to be avoided Fractures are treated in the usual manner and respond well if the scurvy is recognized and treated Hemarthrosis may require special treatment, including, at times, surgical intervention

CHAPTER XXIII

MINERAL DEFICIENCIES

JOHN B YOUMANS

IRON DEFICIENCY

The principal manifestation of iron deficiency is anemia As has been explained in chapter V iron deficiency is only rarely the result of an inadequate intake of iron, rather it is the result of a loss of iron (1) by bleeding (2) in the female by transfer of iron to the fetus and (3) in the child by failure to receive an adequate endowment of iron at birth

There are several reasons why iron deficiency anemia is of particular interest to physicians First it is probably the commonest nutritional deficiency disease seen in practice Second in the majority of cases it is a conditioned deficiency the result of some other disease or occurrence of which the physician has or should have knowledge and hence be forewarned concerning its possible occurrence Third it requires specific treatment with pharmaceutical iron by a physician It cannot be relieved simply by diet

With unusual exceptions iron deficiency occurs under the following conditions

1 In children who have failed to receive an adequate endowment from their mother at birth and whose growth and expanding blood volume require more iron than can be supplied by their inadequate reserve and the diet Normally the mother supplies a reserve sufficient for such growth, in part by a small store of iron in the liver and a larger amount indirectly from the breakdown of excess hemoglobin during the first two and one half to three months much of which is in turn stored in the infant's liver A diet poor in iron may contribute to the occurrence of such an anemia but is not ordinarily the principal cause However the store is depleted sooner with illness The anemia usually appears in the latter part of infancy at the end of the milk diet period, which is low in iron and which the normal infant goes

through without anemia because of his reserve Current practice in feeding provides dietary supplements as early as the second or third month, hence 'milk anemia' now occurs only in babies who have not had suitable supplements and is usually most severe at the end of the first year The severer the deficiency at birth, the earlier the anemia appears, and a progressively diminishing reserve of the mother may be reflected in increasing anemia (microcytosis) of successive children [1]

2 In women who have yielded excessive amounts of iron to their children and commonly in women who have had multiple pregnancies, usually in rapid succession The iron deficiency and anemia may be exaggerated by blood loss and by a diet poor in iron though the latter is not a primary factor

3 In persons who have lost blood Women in the age period from the onset of menses to the menopause make up the largest number in this group because of blood loss at menstruation including abnormal menstruation (menorrhagia and metrorrhagia), and loss of blood at childbirth These losses and the loss to the fetus exaggerate each other in a reciprocal fashion as previously indicated In addition women are subject to the other forms of blood loss which are the causes of the iron deficiency in male subjects Children, too, suffer from loss of iron by bleeding In general, chronic repeated small losses from hemorrhoids, peptic ulcer and ulcerative colitis are the usual causes, but repeated larger hemorrhages can bring about a loss sufficient to cause a deficiency In this group should be mentioned blood donors The loss of iron in those who make donations four or five times a year or more may be such that it is difficult or impossible to replace the iron from dietary sources alone

The anemia of iron deficiency is a microcytic hypochromic anemia, characterized by a decrease in hemoglobin a decrease which is relatively greater than the drop in red cells The most striking picture is that of chlorosis the green sickness now rare with green pallor a very low concentration of hemoglobin but a red cell count not far from normal However in most

1 Guest G M in Nutrition The Newer Diagnostic Methods Proceedings of the Round Table on Nutrition and Public Health Sixteenth Annual Conference March 29 31 1938 New York Milbank Memorial Fund 1938 157 pp

cases the red cell count is considerably reduced (down to 3 000,000) and it may be lower, though rarely as low as in pernicious anemia Hemoglobin values may be as low as 6 or 7 Gm, with a red cell count near normal

On smear, the red corpuscles are faintly stained the most characteristic change With severe lack of hemoglobin the center of the cell may be practically invisible only a rim of pale staining hemoglobin surrounding a central empty i e unstaining area There is often some variation in size and shape though not usually of the degree seen in pernicious anemia The cells are almost always smaller than normal (microcytic) as shown by a measurement of cell diameters and a mean corpuscular volume (M C V) less than 80 cubic microns Mean corpuscular hemoglobin (M C H) is reduced and even more important mean corpuscular hemoglobin concentration is below normal usually much below A reduction in mean corpuscular volume, that is a decrease in the size of the cell (microcytosis) may be the first evidence of the anemia in children[2] Reticulocytes are normal or slightly reduced There may be slight leukopenia, usually with relative lymphocytosis and granulocytopenia. Platelets are normal The bone marrow shows hyperplasia with numerous normoblasts

Patients with microcytic iron deficiency anemia customarily have insidiously developing weakness fatigability and lack of energy and often giddiness or faintness In cases of severer disease are seen the signs of secondary involvement of the heart and circulation, dyspnea on exertion, palpitation and even edema and more pronounced symptoms of congestive heart failure attributable to the combination of overwork and poor nutrition of the heart.

Pallor is the most frequent and characteristic physical sign varying with the grade of the anemia and involving skin nail beds and mucous membranes The conjunctivas and scleras show it especially well as do the tongue and buccal mucosa. The pallor a greenish cast and the anemia constituted the former chlorosis (green sickness) of young female patients

2 Guest, G M Hypoferric Anemia in Infancy in Lejwa A. Symposia on Nutrition of the Robert Gould Research Foundation, 1947 Cincinnati, The Robert Gould Research Foundation, Inc., 1947 vol. 1 p 144

Additional findings in a considerable number of those with iron deficiency are (1) some papillary atrophy of the tongue and (2) an enlarged heart with overactive apex impulse, tachycardia and murmurs, the so-called hemic' and functional' murmurs There may be some hepatomegaly and a palpable spleen Dependent edema, essentially cardiac, may be present Although there may be numbness and tingling of the extremities these are circulatory in origin and there are no objective neurologic changes The finger nails in some patients become brittle rigid and flattened, even becoming con cave, 'spoon nails or koilonychia

In contrast to patients with some of these physical observations, there appears to be a group with cheilosis, stomatitis and glossitis[3] In them there is reddening of the lips glossal and buccal mucosa and, in some fissures at the corners of the mouth The tongue may show fiery red, atrophic glazed glossitis In a still smaller number, there is associated dysphagia, with pharyngitis esophagitis and even web' formations in the esophagus The relation of these changes, at least the cheilosis and glossitis in some of these patients, to iron deficiency seems to have been clearly established by the response to adequate treatment with iron the absorption of the latter demonstrated by the use of radioactive iron[3] and signalized by reticulocytosis Moore has remarked on the apparently greater number of those with these manifestations including koilonychia in the North European countries than in the United States[4]

Achlorhydria is frequent in these patients and of importance in treatment in relation to absorption of iron The achlorhydria may or may not be histamine resistant and is not necessarily permanent, free hydro chloric acid returning after successful treatment of the anemia

Before leaving this description of the nature and clinical characteristics of iron deficiency anemia it is important to note that iron deficiency may and often does occur with other anemia (particularly that of infection) that such combined forms modify the changes

3 Darby W J The Oral Manifestations of Iron Deficiency J A M. A. **130** 830 (March 30) 1946 Waldenst om J and Hallen L. Iron and Ep thel um Some Clinical Observat ons Acta med. Scandinav 1938 supp 90 p 380

4 Moore C V Iron M tabol sm and Hypochrom c Anemia, in Lejwa, A Symposia on Nutrition of the Robert Gould Research Founda tion, 1947 Cincinnati The Robert Gould Research Foundation Inc 1947 vol. 1 p 117

and complicate diagnosis, that relief of the iron deficiency will not cure other forms and that other treatment will not help iron deficiency anemia In diagnosis, care must be taken to distinguish it from other forms of anemia, particularly with the anemia of infection

The statement has already been made that iron deficiency is probably the commonest nutritional deficiency seen in medical practice It may be the commonest nutritional deficiency in the general population It must be remembered, however that such a conclusion may be in part the result of ease and accuracy of diagnosis, even in the slight deficiencies It should be remembered however that a low hemoglobin level alone is not sufficient as an index of the incidence of the deficiency and that there is normally a range of hemoglobin values within which numbers of the various age, sex and other categories fall Studies of the response of the hemoglobin concentration to the administration of iron in connection with surveys of hemoglobin levels of the population are needed to determine the actual incidence of the deficiency

Treatment—The best treatment of iron deficiency (and iron deficiency anemia) is prevention This is particularly true in respect to infants for whom prevention means the prevention of iron deficiency in the mother during pregnancy by the administration of supplemental iron

As stated previously iron deficiency and iron deficiency anemia cannot be cured by diet Iron must be given in pharmaceutical form In practice this is true for prevention in the mother The iron must be given in adequate dosage and adequate dosage means several times more than that which will be absorbed The presence of an excess aids absorption When there is a real need and adequate treatment is given response is specific and barring complications satisfactory The response is marked by reticulocytosis which checks the diagnosis Treatment should be continued until the full benefit is obtained (normal size in children)

The best preparation is ferrous sulfate and the dosage 0 3 Gm three to four times daily Other preparations are ferrous chloride carbonate or gluconate used in equivalent iron (Fe) dosage iron ammonium citrate 2 Gm three times a day and metallic (reduced) iron 1 Gm three times a day Occasionally it is necessary to use somewhat larger doses

Proportionately smaller doses are used for infants and children Ferrous sulfate is best for use in a formula Traditionally, patients complain of gastro intestinal symptoms, nausea, cramps diarrhea and epi gastric distress, from taking iron but if they persist in continuing treatment, these symptoms usually dis appear Sometimes they are able to take one form rather than another but this probably represents the same acquired tolerance and a tolerance which would have developed had they continued with the same preparation

Parenterally used preparations are in general unsatis factory[5] The toxic dose is too close to the effective dose, and reactions which may be severe are frequent Iron is a strong poison This is particularly true of iron injected intravenously, which is only rarely justified

The concomitant use of hydrochloric acid in adequate doses (4 ml well diluted during meals) for patients with achlorhydria is often advised as an aid to absorp- tion of the iron Its effectiveness is disputed but clini cal observation suggests that it is helpful (Perhaps it may lessen the gastrointestinal discomfort and hence *encourage the patient to take the iron*)

Two other measures are important One is to dis cover and control any chronic bleeding Increasing the intake of iron while it is being continually lost is usually ineffective The other is use of tranfusions These are particularly helpful to provide a quick start or boost toward a normal level and for patients who persist in their inability to take iron However, when reliance is placed on transfusions, there is a tendency to stop before complete recovery is secured, in part one of the principal errors in the treatment of iron deficiency is a failure to continue treatment to the stage of complete recovery

There is no benefit from the use of copper for adults and only rarely for infants *Other metals vitamins* and many other preparations sometimes recommended are ineffective and a needless expense and trouble

The reticulocytosis following adequate treatment (and a correct diagnosis) appears in about three to five days and reaches the usual peak in six to ten days then as in other anemias the reticulocyte count becomes normal Hemoglobin begins to increase about this time

5 Darby W J The Handbook

and increases about 0 15 to 0 3 Gm per hundred milli liters until the curve flattens out as normal values are approached This is a critical time from the point of view of continuation of treatment until full recovery occurs The red cells if reduced, follow the hemoglobin curve In children increase in cell volume is important and symptoms respond quickly

CALCIUM

It is somewhat difficult to discuss calcium deficiency disease apart from a deficiency of vitamin D The two are so interrelated that to some extent a deficiency of both may be considered to constitute a single disease This is not altogether true however, for in adults the interdependence is less close than in children and in the latter the deficiency of calcium may be considered and often is a relative deficiency one which would not be a real deficiency were it not for the existence of the deficiency of vitamin D

Nutritional calcium deficiency is recognized clinically as osteomalacia in the adult The osteomalacic changes in the child are so related to accompanying rickets present in nearly every case that it is difficult to separate them clinically

Classic examples of primary nutritional osteomalacia (due to calcium deficiency) are rare in this country and are largely confined to pregnant women or women who have had many pregnancies Conditioned deficiencies, such as occur in sprue from the loss in the stool of calcium bound to the unabsorbed fat are commoner Together with the deficiency of calcium occurring with hypoparathyroidism the patients have the symptoms physical signs and laboratory findings of the severer deficiency of calcium these enable one to deter mine that such cases of nutritional calcium deficiency are *infrequent*

Vitamin D appears to play an important role in regulating the absorption of calcium from the intestine It is unlikely that a shortage of vitamin D occurs frequently in the adult It may be a factor in border line cases of dietary calcium deficiency Other factors affecting absorption are (1) the relative and absolute proportions of calcium and phosphorus in the diet (2) the availability of dietary calcium not all being equally absorbable (3) the acid base reaction of the

diet and the presence or absence of hydrochloric acid in the stomach (the presence of the acid favors absorption, and a diet increasing body alkalinity when burned in the body favors deposition of calcium), (4) factors other than vitamin D, causing greater or less absorption and loss and (5) factors affecting the general metabolism Examples of the latter are pregnancy lactation and disturbances in hormonal regulation such as that of the adrenals, following bodily injury All these factors must be given full consideration when primary nutritional osteomalacia is considered, as must the now well recognized dynamic nature of the mineral deposits in bone, which even in adult life are in a constant state of adsorption (or deposition) and resorption

Pathology—The pathologic changes in calcium deficiency are to be found principally in the bones, the concentration of calcium in the blood, abnormalities in the excretion and retention of calcium and if the loss of calcium is great enough functional neuromuscular abnormalities (tetany) The latter is extremely uncommon, and nearly all calcium tetany is the result of lowered calcium in the blood from causes other than calcium deficiency In calcium deficiency the decreased intake or absorption, leads to a negative calcium balance and more calcium is excreted or lost than is taken in This results in a withdrawal from the skeleton Studies of rachitic and osteomalacic bones have shown that there is a reduction in total bony substance as well as simply a decrease in the calcium content Histologically there is an increase in the amount of osteoid tissue and a decrease in the amount of true bone The result is that the bone becomes softened and more pliable Because of the influence of weight bearing the pelvis spine and lower extremities are affected principally in adults (In young children other bony structures may be the ones to be affected more severely) As a result of this softening deformities often severe develop Roentgen examination of the skeleton reveals demineralization if the deficiency has been severe or of sufficient duration However it is difficult to detect slight or early demineralization and to distinguish it from other forms of demineralization that accompanying old age for example

Calcium is also involved in various enzymatic and biochemical reactions including the clotting of blood

There is little likelihood however that these functions are more than rarely affected The reason for this is clear in view of the small amounts of calcium needed for these functions and the relatively large store of calcium in the skeleton on which they probably have first call Only in the severest deficiencies and most advanced softening of the bones would interference with these functions be expected At the present time bleeding or a deficiency in blood clotting can only rarely be considered a result of calcium deficiency

The exact relation of calcium to dental caries is not clear The teeth are a part of the skeleton and might be expected to be affected in some manner or other in a calcium deficiency affecting bone

Calcium deficiency causes a disturbance in formation of the teeth in experimental animals and presumably is a factor in humans[6] The mechanism of caries formation is so complex however that it is difficult to assign a clearcut role to the influence of a deficiency of calcium From a practical point of view however the probability of significant relationship is sufficiently great to warrant the protection of supplemental calcium for persons such as pregnant and lactating women

Clinical Manifestations—The symptoms and signs of severe calcium deficiency are as well known as they are rare With the osteomalacia pain is almost always present and severe It is deep seated aching or 'boring' in character commonest in the back chest and sacroiliac regions, and frequently radiates along the course of the spinal nerves It is usually unaffected by motion except when there are fractures These are commonest in the vertebrae (compression fractures) and are often unsuspected being disclosed by roentgen examination There may be knuckling and noticeable loss of stature The pelvic deformities often remaining after recovery from an attack are well known as a complication of pregnancy but fortunately, are now uncommon Other deformities occur in the thoracic cage There is usually considerable muscular weakness in severe osteomalacia

The symptoms and signs of tetany are well known Latent tetany may be demonstrated by the presence of Chvostek s or Trousseau s sign The first is a quick contraction and irregular muscular twitches of the

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6 Meiklejohn, A. P Diet and Dental Health, Edinburgh M. J 56:41 1949

facial muscles following a light blow with the finger or reflex hammer over the facial nerve Trousseau's sign is the *main d'accoucheur,* or "obstetrician's hand," an adduction of the hand with the fingers flexed at the metacarpophalangeal joint but extended at the interphalangeal with a strongly flexed and adducted thumb when the circulation in the hand is obstructed for a short time with a tourniquet An increased sensitivity to the stimulus of the galvanic current, Erb's phenomenon, also may be elicited in latent tetany Chvostek's sign is less common and less easily elicited in adults than in children

Manifest tetany *presents* the well known picture of carpopedal spasm tetanic facies and, frequently, frank convulsions the latter especially in children Laryngospasm and inspiratory apnea may occur

Diagnosis—The signs and symptoms of early or mild calcium deficiency are ill defined and unreliable An aching pain in the extremities more noticeable at night, seems to be one of the commoner signs Pain in the chest associated with a spontaneous fracture may be one of the presenting symptoms Sometimes the condition is suspected from a chance roentgenogram Tenderness of the spine may be elicited Tetany does not occur with this grade of deficiency and changes in the concentration of calcium in the blood are of questionable significance

The diagnosis of mild osteomalacia depends on the history of a diet possibly inadequate in calcium (especially with increased loss or demand) inadequate exposure to sunlight or inadequate intake of vitamin D *symptoms principally pain and demineralization* detectable in roentgenograms of the skeleton *All these are suggestive only and require support* from the therapeutic trial If the condition is truly osteomalacia caused by a lack of calcium it should respond to the administration of calcium In practice vitamin D is generally given with the calcium

In the severer cases the diagnosis is easier and more certain Pain is severe and the deformities are often obvious Demineralization as shown roentgenographically, is obvious The blood serum usually reveals an elevated alkaline phosphatase level and some drop in the concentration of calcium The latter is con

sistently low if tetany is present Normal standards for alkaline phosphatase are generally accepted as 3 to 12 Bodansky units for children and 3 to 5 for adults The significance and relationship of variations in alkaline serum phosphatase in adults or, particularly, in adolescents are not well known Normal values for calcium in the blood range from 9 to 11 mg per hundred milliliters in adults and from 10 to 11 mg in children

Great care must be taken not to confuse simple calcium (or calcium and vitamin D) deficiency with other disease The symptoms of the former are unreliable and the tendency is to put considerable reliance on roentgen changes in the skeleton Too often recently these have been uncritically interpreted as the result of a lack of calcium There are several causes of demineralization or decalcification One of the commonest mistakes is to interpret the demineralization found in elderly women sometimes with pathologic fractures, as primary calcium or calcium and vitamin D, deficiency This may be the cause in some cases but in most of them the deficiency seems to be related to an endocrine factor accompanying or following menopause Not all senile demineralization is calcium deficiency, though many patients with senile demineralization would appear to be ideal subjects for such a diagnosis Demineralization occurs with chronic illness of various sorts especially that involving bedrest Other and usually severer demineralization is seen with parathyroid disease and with chronic nephritis In these conditions the serum calcium level instead of being lowered is elevated and phosphatase activity greatly increased

Incidence—The incidence of calcium deficiency is unknown It is unlikely that an actual pathologic deficiency of a primary type even combined with a vitamin D deficiency is frequent Certainly it is infrequent in adults if care is taken not to include incorrectly the mild grades of demineralization found in older persons especially women

Special consideration however, must be given to its occurrence in children, particularly older children and older adolescents Growth poses additional demands and constitutes a 'stress which may result in a deficiency Infants and children, who are likely to

consume considerable amounts of milk, are less likely to suffer calcium deficiency than somewhat older children The latter and adolescents as a group are less likely to receive milk in protective amounts and may be somewhat more in danger of a deficiency of calcium

Treatment—The treatment of primary nutritional calcium deficiency is the administration of sufficient calcium In practice, vitamin D is usually added to promote adsorption In many mild cases (without pathologic fractures severe demineralization or similar advanced changes) calcium can be supplied to advantage simply as milk with or without vitamin D For severer cases (without tetany) calcium chloride cal cium lactate or calcium gluconate can be used One to 2 0 Gm of calcium daily for children and 2 0 to 3 0 Gm for adults will usually suffice The amount of calcium varies with the different compounds, 33 per cent by weight for the chloride 23 per cent for the lactate and only 10 per cent for the gluconate Hence the actual dose will be 3 to 6 Gm of the chloride and 4 to 8 Gm of the lactate for children and 6 to 9 Gm of calcium chloride and 8 to 12 Gm daily of calcium lactate for adults or older children Calcium lactate is to be preferred over the chloride, and the phosphate is useful for children because of the need for additional phosphorus to accompany the calcium The gluconate is useful for parenteral administration if needed, which is uncommon

Tetany demands more energetic measures Calcium should be given both orally and parenterally Cal cium gluconate[7] 1 0 Gm given intravenously two or three times a day, is advisable with calcium by mouth until the tetany is relieved Large doses of vitamin D should be given with the calcium Sometimes it will be advisable to use acidifying drugs such as ammonium chloride to promote adsorption and to increase the serum calcium to a normal concentration This more drastic treatment is needed not for eventual relief but to hasten recovery and prevent serious complications

It may not be amiss to point out that tetany may be precipitated by treatment of severe rickets with the vitamin D

7 Calcium chloride if used must be given with the caution required for the use of this drug intravenously

IODINE DEFICIENCY

Aside from whatever doubts may be raised respecting iodine deficiency as the cause of endemic goiter,[8] it can be confidently stated that simple goiter and endemic cretinism are the clinical manifestations of iodine deficiency Iodine is essential to normal growth development and health It cannot be synthesized by the body and must be obtained from without Lacking it there is a deficiency in the formation of the essential hormone thyroxin the thyroid gland enlarges and goiter with its accompanying altered functions if any, structural changes symptoms and physical signs, develops

Two principal pathologic conditions result from the lack of iodine—goiter and hypofunction of the thyroid gland (hypothyroidism)—one structural the other functional Both or either one may be present, but when hypothyroidism is due to iodine deficiency it is usually accompanied with a goiter The two conditions should be sharply differentiated because of the difference in their effects Goiter can exist without any interference with body function or any untoward effect except a cosmetic one or such as may be caused by a localized tumor Hypothyroidism affects many body functions and the growth and activity of all tissues In its severest form it results in greater or lesser grades of cretinism Sporadic cretinism—i e. athyroidism the result in all but the rarest instances of something other than iodine deficiency—should be distinguished from cretinism due to iodine lack

The pathologic structural expression of an inadequacy of iodine then is simple goiter and if the iodine deficiency is continued through generations endemic cretinism The latter is seen almost altogether in goitrous regions Similarly an older child or an adult could conceivably take in so little iodine over so long a period that hypothyroidism would develop Adult myxedema however differs from simple hypothyroidism and is almost always due to causes other than iodine deficiency.

Pathology—Simple goiter is an enlargement of the thyroid gland (hyperplasia and hypertrophy) It

8 Greenwald I Is Endemic Goiter Due to a Lack of Iodine? J Clin Endocrinol 6 708 1946 Kimball, J Correspondence J Clin Endocrinol 7 58 1947 Relation of Endemic Goiter to Lack of Iodine, Nutrition Rev 6 40 1948

results from the strain imposed by attempts to manufacture thyroxin with an inadequate supply of iodine It is important to know that this enlargement does not of necessity mean a deficient production or secretion of the thyroid hormone Means[9] has expressed it as follows 'The factory may be working under difficulty, the supply of raw material decreased, overwork and additional machinery may be needed, but until the supply of iodine is used up hormone in essentially normal amounts is furnished" Only when the supply of iodine becomes absolutely inadequate does the supply of hormone to the tissues become insufficient Only then do the pathologic changes and symptoms of hypothyroidism as well as goiter, appear with cretinism as the severest grade appearing ordinarily only after generations of iodine deficiency hypothyroidism Children born of goitrous (iodine deficient) *mothers will be likelier to have goiter* their children have an even greater tendency to goiter and so on until cretinism develops Cretins may present goiters

As with other nutrients and nutritional deficiencies the deficiency of iodine may be *absolute or relative* Secondary factors may 'condition' an iodine deficiency For iodine in contrast with most other nutrients the deficiency is probably most often absolute Only in areas of border line iodine supply or in individual instances does relative iodine deficiency appear to be operative Secondary factors are many Body size, rapid rate of growth puberty pregnancy and possibly menstruation are physiologic causes for an increased demand With a safe margin of intake they are ineffective in producing a goiter With border line intakes, they may cause relative insufficiency Infections and pollution of water or food have been thought by some to be concerned but such mechanisms have not been clearly demonstrated However a relative shortage caused by an excessive demand for thyroxin by the tissues is a possibility For example certain foods can produce goiter in animals The organic cyanides in certain vegetables depress tissue oxidation and cause a demand for more thyroxin[10] Such goiters can be prevented by administration of iodine Whether such a factor is operative in humans is unknown Other

9 Means J H The Thyroid and Its Diseases ed. , Philadelphia, J B Lippincott Company 1948
10 Salter W T The Chemistry of the Hormones Ann R v Biochem. 14 561 1945

goitrogenic agents cannot be inhibited by iodine A relative insufficiency of iodine from difficulty of absorption is probably uncommon if it exists Iodine is readily absorbed

The deficiency of iodine which will result in recognizable changes in the thyroid gland has been accurately determined When the concentration of iodine in the thyroid gland falls below 0 1 per cent (dry weight), hyperplasia occurs Such an expression is of no practical value clinically It does however express the reserve of hormone or iodine which the thyroid maintains and when the reserve falls below this level, more hormone or iodine must be stored If the iodine supply is too small to allow it to be extracted from the blood by the normal gland, hyperplasia and hypertrophy develop to further that process The result is a goiter

The morphologic changes in a goiter caused by a deficiency of iodine vary both grossly and microscopically with the various stages of the disease and the effect of secondary changes In the beginning the gland enlarges symmetrically and becomes softer and more vascular The cut surface appears more cellular Colloid is decreased Microscopically the epithelium changes from low cuboidal and cuboidal to high cuboidal or columnar Stored colloid is decreased, vascularity is increased Analysis shows a decrease in iodine The follicles become infolded with papillary projections into the lumen, and no longer are normal or oval but are irregular in outline Cells show increased mitosis

This is the stage of active hyperplasia and hypertrophy It does not differ from the physiologic hyperplasia of pregnancy or puberty or that of other physiologic conditions of increased demand for hormone It constitutes the first stage of the thyroid cycle of Marine

The next stage as defined by Marine[11] is either atrophy or involution If the deficiency of iodine persists, the overworked cells eventually atrophy and die The alternative to this apparently commonest in this country because an adequate supply of iodine becomes available before much atrophy can occur, is involution Involution is a reversal of the changes seen in hyperplasia and hypertrophy The gland becomes redder and firmer The blood supply diminishes Colloid

11 Marine D The Pathogenesis and Prevention of Simple or Endemic Goiter J A. M A. 104 2334 (June 29) 1935

again fills the follicles, even overfilling and disturbing them The epithelium shrinks to cuboidal and low cuboidal, the stroma becomes less prominent The iodine content of the gland increases Opinion differs as to whether the gland ever returns completely to normal after such an experience Marine thinks not and believes that the colloid phase is the nearest approach to normal such a gland can reach This is undoubtedly true in many cases, and the enlarged gland with overdistended follicle filled with colloid constitutes what is commonly known as a colloid goiter

Such a result however, is an incomplete involution Clinical experience teaches that many hypertrophic and presumably hyperplastic glands due apparently to absolute or relative iodine deficiency, may return completely to normal (the goiter disappears) This indicates that such is the normal course of involution, and failure to do so indicates arrested involution One possible explanation for the latter may be as Means suggests a change in colloid stored too long which makes it incapable of resorption This may be the case in old large endemic, colloid goiters

After complete involution and return to normal, there may again be iodine deficiency, relative or absolute The gland then again becomes hypertrophic and hyperplastic perhaps once again to involute According to Marine this cycle often is repeated several times With each cycle the return to normal becomes less likely If the gland fails to return to normal the first time or at subsequent periods each period of partial involution and colloid overretention makes the goiter a little larger Furthermore, during involution especially incomplete involution localized areas of the gland may fail to resolve and become overly distended with colloid thus causing nodules Nodules may undergo a variety of secondary changes They may become cystic become surrounded by dense fibrous tissue, become calcified or undergo other degenerative processes Discrete nodules composed of hypertrophied and hyperplastic tissue without colloid or with small amounts occur in some cases, perhaps because of local interference with the circulation The smooth' type of goiter is common in children and younger adults Nodular goiters come with advancing years and may be related to such stresses as childbearing

In cretinism, in contrast to simple goiter, there are widespread changes throughout the body, as well as severer injury to the thyroid The latter may show changes varying from complete or nearly complete absence to massive goiters which show the microscopic changes of the milder simple goiter However in the cretin, despite the development of a goiter (hypertrophy), there is a greater or lesser failure of function sufficient to cause general effects on the body Usually the function of the thyroid is poor The persistence of some function explains the varying degrees of cretinism and in this respect distinguishes endemic from sporadic (athyreosis) cretinisms in which the loss of function is nearly always complete Juvenile myxedema lies between the two Means defines the latter as a state of athyreosis acquired by a previously normal child prior to the attainment of puberty and full growth It is rarely caused by iodine deficiency

In the thyroid of the cretin the changes consist of replacement of normal structures by fibrous tissue, with scattered follicles some of which may contain colloid In cases of less severe disease one sees atrophy of secreting cells and an infiltration with lymphocytes and plasma cells which form an outline of the former follicle

The general body changes are primarily those of retardation in development Included are delayed epiphysial union delayed and imperfect ossification faulty and delayed dentition and incomplete cerebral development A significant observation in relation to the existence of a thyrotropic hormone is a rather frequent hypertrophy of the anterior lobe of the pituitary

Clinical Manifestations—Except for cretinism the principal and as a rule the sole manifestation of iodine deficiency is a (simple) goiter and the only signs and symptoms are those associated with the goiter In goiters developing earlier in life the child presents at 5 or 6 years of age a fulness in the neck first palpable and then visible It is smooth soft, symmetric and without tenderness or evidence of increased vascularity The child may have a sense of fulness but usually the goiter is first noticed when it becomes visible to the family The child otherwise is essentially normal In more goitrous regions there are more and larger goiters at younger ages, but large goiters are usually

found in older children The incidence is greater in girls With advancing age (beyond puberty) some of the goiters disappear, many become smaller These changes are commoner in boys Girls are likelier to have an increasing incidence and an increase in size up to the age of 17 or 18, and the goiters disappear less often Pregnancies have an important effect in increasing the size of the goiter As the goiter becomes smaller it becomes firmer, but it may become larger as it gets firmer (colloid storage)

A temporary enlargement occurs in girls and women with menstruation and other factors, such as infections other diseases and emotional stress, can cause temporary enlargement This is not ordinarily a true pathologic enlargement although it is possible that some of these are the result of a temporary, relative iodine deficiency and hence are true iodine deficiency goiters in a strict sense

Aside from the appearance and perhaps a slight sense of fulness, which may be exaggerated, these goiters cause no symptoms Large goiters may cause pressure on neighboring structures, but this is uncommon in young persons in this country

In the middle and later years, the goiters show an increasing tendency to become nodular This causes more frequent pressure effects and is associated with the complications described under pathology There may be pressure in the trachea with deviation compression and interference with respiration, even complete obstruction With this there may be cough, difficulty in swallowing, venous obstruction, edema of the face and pressure on nerve trunks Nodules may become cystic with hemorrhage into them causing pain and swelling Infection may cause suppuration, and there is a tendency to malignant degeneration

As already stated disturbances in function are uncommon but occasionally there may be a mild grade of hypothyroidism (as distinguished from true cretinism) This is usually detectable only by a determination of the metabolic rate and the response to thyroid (it does not ordinarily respond in a simple clearcut fashion to iodine) Symptoms are slight and usually nonexistant but there may be some sluggishness fatigability lack of interest and energy and poor attentiveness Examination shows little but the goiter and

perhaps some pallor There may be a mild, related anemia

The clinical features of cretinism are well known Most cretins are imbeciles from birth and are usually born with goiters If treatment is not begun early in life they respond poorly to thyroid and not at all to iodine They exhibit characteristic facies, disturbances in growth and character of the hair, thick, enlarged portruding tongues, faulty dentition, failure and disturbances in maturation and growth which are characteristic

Diagnosis—The diagnosis is usually made by the detection of the goiter, which means that the iodine deficiency, *responsible for and existing before the* goiter, was neglected A deficient intake of iodine can of course, be recognized in areas of endemic goiter and has been for years It is difficult or impossible in sporadic cases and particularly with respect to relative deficiency of intake Hence the importance of prevention, which is, of course, well recognized in relation to endemic goiter In individual cases the physician should be alert to the possibility of deficiency in his patient's diet and to the presence of possible contributory or conditioning factors such as pregnancy

It is necessary to distinguish between simple goiter and other kinds of goiter The simple goiter in young persons is diffuse, symmetric and usually without nodules It is soft The borders of the lobes are difficult to identify, and it moves readily in swallowing There are no bruits or thrills In the older children and young adults it is usually more firm and at still later ages, often nodular The principal differential diagnosis is between it and so called toxic goiter (Graves disease, exophthalmic goiter, goiter with hyperthyroidism) Signs and symptoms of thyrotoxicosis particularly an elevated basal metabolic rate, are incompatible *with simple goiter However thyrotoxicosis* occurs at all ages and may develop in patients with simple goiter Malignant new growths can occur in simple goiter and may cause difficulty in diagnosis especially if the simple goiter has nodules Changes in consistency attachment to surrounding tissues, lack of mobility and metastases are characteristic of malignant growths Thyroiditis may cause enlargement of the gland (goiter) but is characterized by pain, heat,

tenderness and signs of local inflammation sufficient to distinguish it from simple goiter, although simple goiter may become inflamed Hyperthyroidism is ordinarily detected only by determination of the basal metabolic rate

Incidence—As is well known, the incidence of iodine deficiency and simple goiter and other sequelae varies with the iodine content of the soil and water In some regions it is so low that iodine deficiency, unless relieved by special procedures, is almost universal In others the supply is so great that iodine deficiency and goiter occur only sporadically and as a result of special conditioning factors In this country there are goitrous areas but none so severe as in certain parts of Europe and Asia The former includes the Northwest states, the Great Lakes region and Colorado The general range of incidence according to Olesen, is from 10 to 27 goiters per 1,000 population to 1 per thousand There may be local areas with a much higher incidence Modern prophylaxis has greatly reduced the occurrence of iodine deficiency and the number and size of goiters

Treatment—The prevention of iodine deficiency and the resultant goiter is relatively easy and highly successful treatment of the goiter is not Hence prevention is important Mass prevention is highly desirable and important and is best accomplished by the use of iodized salt If necessary, it can be used on an individual basis Ten grams of the iodized salt used in this country will provide 0 1 mg (100 micrograms) daily The requirement is usually considered to range between 0 02 and 0 075 mg (20 to 75 micrograms) If other forms of iodine are preferred for individual use it may be given as sodium iodide syrup of hydriodic acid, tincture of iodine or other preparations One drop of strong iodine solution U S P per week is satisfactory This provides about 243 micrograms per day which may be provided satisfactorily for children for three or four weeks in spring and fall Larger amounts than those indicated are sometimes recommended and are harmless but unnecessary The fear of inducing thyrotoxicosis, even in nodular goiters, I believe, is groundless

General hygiene and diet should be considered in the prevention of goiter There is an advantage in the inclusion of fresh vegetables but the goitrogenic action of some, such as cabbage and related vegetables, must

be considered Avoidance of infectious disease is beneficial Certain persons, particularly pregnant women and pubescent children (especially girls), require special protection This will be most needed in regions where the iodine supply is border line or minimal and where general prophylaxis is not practical However, it is difficult to suspect sporadic cases and it is best that all pregnant women receive a supplement of iodine especially in the latter half of pregnancy The dose and amount of strong iodine solution mentioned previously is satisfactory The use of iodized salt for all children is desirable but where it is not used the physician should keep close watch of the children under his care

Small goiters may be treated with iodine with the possibility that they will be reduced in size Some will completely disappear Somewhat larger doses of iodine 1 to 5 drops of strong iodine solution U S P a day for two to four weeks repeated at intervals of three or four weeks over a period of six months or a year, may be tried Equivalent amounts of other preparations can be used The treatment may be continued at intervals over a longer period In some cases this treatment will make the gland somewhat larger and more tense or firm This may cause the patient or the family some concern but is rarely of any significance and usually is in turn followed by a decrease in size The increase in size and firmness, which is the result of laying down of colloid is not seen more often because it has usually occurred before the patient is seen by the doctor Nodular goiters respond poorly if at all to iodine and usually require surgical treatment Sometimes the nodules are made more prominent by treatment with iodine They become apparent or more prominent when the other surrounding portions of the gland have undergone involution after treatment with iodine The patient may consider this an unfavorable result and the possibility of such a change must be considered in the treatment of such patients

No untoward effects from iodine are to be expected except in the iodine sensitive patient. Occasionally iodine will cause a drop in the basal metabolic rate of persons with simple goiter It is only temporary and is without any harmful effect

Thyroid (extract) is sometimes used in simple goiter on the basis that the hyperplasia and hypertrophy can

be relieved by an exogenous supply of the thyroid hormone Such treatment is sometimes effective in the early stages and may be tried in selected cases It should be combined with the use of iodine It is especially useful in patients who have associated symptoms of hypothyroidism and a lowered basal metabolic rate Recently thyrotropic hormone, which stimulates thyroid function and leads to a loss of colloid from the gland, has been suggested for the treatment of simple goiter Theoretically its use is logical, and it may be tried in selected cases Because of its diminishing effectiveness on continued use it is unlikely that careful administration will cause harmful overstimulation

Surgical removal is the only satisfactory treatment for larger goiters and may be needed, even urgently, for smaller goiters with pressure symptoms However, in general, surgical treatment should be withheld until adulthood except when pressure symptoms require it

Most small, relatively inconspicuous goiters should not be removed Childhood, puberty and adolescence are periods of intermittent stress and strain, involving interrelated endocrine functions Premature or unnecessary removal may result in a more disfiguring enlargement of the remaining fragments or even myxedema At a later period when the gland is more stable removal in selected cases gives satisfactory results and may be good prophylaxis against cancer Also removal prevents such complications as hemorrhage into cysts

Part IV

FOODS AND THEIR NUTRITIONAL QUALITIES



CHAPTER XXIV

ADEQUACY OF AMERICAN DIETS

ESTHER F PHIPARD
and
HAZEL K STIEBELING

For a long time food has been front page news In many countries of the world the chief concern has been enough food Calories have assumed new importance in scientific economic and political fields It is only in countries like the United States with abundant food supplies that chief attention can be focused not on ' how much food but on how good' are the diets of the people

An ideal report on the adequacy of American diets would be based on periodic and detailed studies of food consumption in a cross section of the various population groups and on parallel investigations of the nutritional status of the people consuming this food Such data are not available at present, hence information of many kinds must be put together to give an indication of the situation This chapter deals chiefly with food supplies and the factors affecting their distribution among various groups and with the importance of, and some of the opportunities for improving dietary levels in the United States

TRENDS IN FOOD CONSUMPTION IN THE UNITED STATES

Trends in the consumption of some major groups of foods are shown in the accompanying charts [1] One of the most decided changes and one of great importance for improved nutrition is the increased use of milk Reenforcing the upward trend since 1909 in the con sumption of milk products such as cheese ice cream

[1] Consumption data prepared by the Bureau of Agricultural Economics United States Department of Agriculture.

and evaporated and dried milk, the use of fluid milk rose sharply during the early war years (chart 1) In terms of total milk equivalent, consumption of milk and its products other than butter averaged nearly 3 cups per day per person in 1945—as compared with less than 2 cups in 1909 As a result there was an increase of 40 per cent in the calcium content of the per capita food supply and a considerable increase in riboflavin

Consumption of citrus fruit (chart 2) and of leafy green and yellow vegetables (chart 3) also has shown an upward trend during these years More than four times

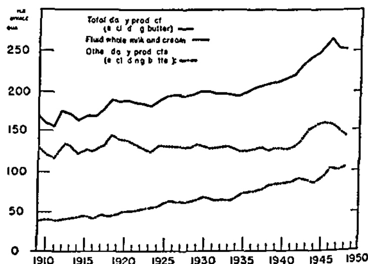


Chart 1—Dairy Products excluding butter per capita consumption in the United States 1909 1948 (Estimates of the Bureau of Agricultural Economics United States Department of Agriculture)

as much citrus fruit was consumed in 1945 as in 1909 Yearly per capita consumption of meat poultry and fish averaged 165 pounds (75 Kg) or more (retail weight) in the period 1944 to 1947 compared with 137 pounds (62 Kg) in the prewar years 1935 1939 (chart 4)

While we have been eating more of some foods we have eaten less of others Consumption of grain products and potatoes has declined considerably since 1909 although the downward trend was arrested during the war years when supplies of fat and sugar were somewhat restricted

The net effect of these shifts in consumption is shown in estimates of the nutritive value of the per capita food supply Trends over a thirty nine year period are shown in chart 5 in available supplies of calcium, iron and of five vitamins for which the National Research Council has suggested daily allowances At the close of the war the calculated quantities of most nutrients were higher than at any time during the thirty nine year period For calcium the increase has been continuous The similarity in the trends of calcium and

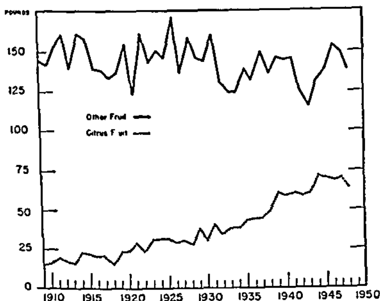


Chart 2—Fru t per capita consumption in the Un ted States 1909 1948 (Estimates of the Bureau of Agricultural Economics United States Depa tment of Agriculture.)

riboflavin up to 1943 reflects the fact that milk is the most outstanding single food source of both, it has contributed from two thirds to three fourths of the calcium and nearly half the riboflavin in the national diet After 1943 riboflavin increased more sharply than calcium because of its use in the enrichment of flour and bread

For several nutrients the most striking increase has come since 1940 Higher levels of vitamin A (as carotene) as well as of ascorbic acid can be associated with the increased consumption of vegetables and fruits The greatest increases were in thiamine niacin ribo

flavin and iron, which were higher by a third to a half than the prewar levels About half of these increases were the result of the enrichment of flour and bread The great similarity in the trend lines for these three nutrients is associated with their occurrence in foods Two groups—grain products and meat, poultry and fish—furnish about half the iron and thiamine and about two thirds of the niacin in the per capita food supply

The peak years in average nutrient levels were 1945 and 1946, with 1948 somewhat lower Compared with

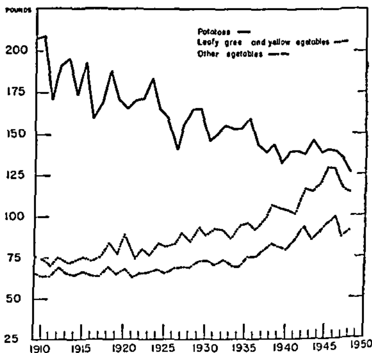


Chart 3 —Vegetables per capita consumption in the United States, 1909 1948 (Estimates of the Bureau of Agricultural Economics United States Department of Agriculture)

those of most countries of the world these levels were exceedingly liberal and they indicate a decided improvement over prewar levels in the United States as shown in table 1 In 1935 1939 the national food supply did not furnish enough calcium to provide for every person in the country the quantities recommended by the National Research Council even if it could have been equitably distributed Also margins for the B vitamins were small compared with recommended amounts

As they are now made, estimates of the nutrient content of the national food supply tend to be high. The large excess of calories over estimated needs indicates something of the waste factor inherent in these figures. Food waste often is especially large in institutions and public eating places, but may also be considerable in households in upper income groups.

For other nutrients apparent margins of supply over need should be generous, for foods and nutrients are seldom distributed in accordance with need among the

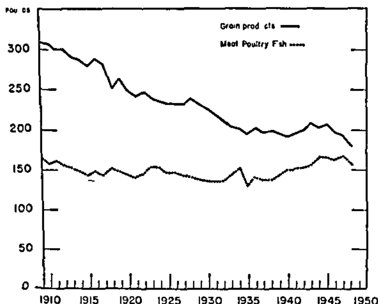


Chart 4.—Meat, poultry, fish, grain products: per capita consumption in the United States, 1909-1948. (Estimates of the Bureau of Agricultural Economics, United States Department of Agriculture.)

persons in a family or among the families of a nation. Large numbers of persons probably get less than optimal quantities of one or more nutrients. Others have diets providing much larger quantities of some nutrients than the allowances suggest. If these latter groups continue to enjoy their liberal diets and if all those who consume less than recommended quantities were brought up to those levels, nutrient averages for the country as a whole would be much higher than they were in 1945 and 1946.

These facts should be kept in mind in any comparison of the nutrients in the per capita food supply with

recommended dietary allowances Other factors to be considered are those involved in any comparison of the calculated nutrient content of a diet with recommended allowances For example most tables of food composition suitable for use with foods as purchased make no allowance for losses that occur in home storage or in preparation for eating For ascorbic acid and some

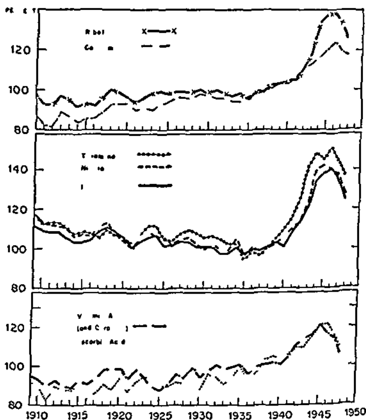


Chart 5 —Calcium iron and vitamins in the United States per capita food supply 1909 1948 (index numbers 1935 1939 = 100) (Computed by the Bureau of Human Nutrition and Home Economics United States Department of Agriculture.)

of the B vitamins which are water soluble heat labile and readily oxidized these losses may be very high On the other hand, recommended dietary allowances represent quantities to be ingested They are considered high enough to cover substantially all individual variations in the requirements of normal persons" However much more needs to be known about variations in requirement about the utilization of nutrients in the

body and the possibility of synthesis of certain vitamins in the intestinal tract before a close evaluation of dietary adequacy can be made on the basis of dietary calculations and recommended allowances

INEQUITABLE DISTRIBUTION

Spot studies provide evidence that even in the peak years of supply, 1945-1946 many families did not have nutritionally good diets In the summer of 1945 the Bureau of Human Nutrition and Home Economics obtained data regarding diets of families living in the open country in one county in Georgia and in one in Ohio In the Georgia county the food of one third of the white farm families and of two thirds of the Negro families provided less than two thirds of the dietary allowances recommended by the National Research Council, for one or more nutrients The prevalence of such unsatisfactory diets was twice as high among sharecroppers and farm laborers as among owners and renters, it was somewhat higher among large than small families in the same income class

Among Negro families in the Georgia county vitamin A was the nutrient that most often seemed to be comparatively low in the diet More than half of the families had food that provided less than two thirds of the recommended amounts A greater consumption of green or yellow vegetables of whole milk, butter or vitamin A fortified margarine would have increased the vitamin A value of diets About a fourth of the families had food that furnished less than two thirds of the recommended levels of calcium and ascorbic acid and the diets of nearly a fifth were correspondingly low in riboflavin More milk and more vitamin C-rich fruits and vegetables would have improved the diets with respect to these nutrients also

It is true in general that farm families are relatively well fed because they can and do raise so much of their own food supply However there are wide differences in the suitability of individual farms for producing different kinds of food Farm tenure makes a difference also Farm owners and renters are more likely to have extensive programs of food production for household use than are sharecroppers and tenants

In the Ohio county where income levels were some what higher and a greater proportion of the farm

families were owners, family diets were somewhat better than in the Georgia county

Money for Food—Too little money for food is still a major cause of poor diets In the Georgia county studied four fifths of the open country families had net money incomes of less than $1 000 in 1944 1945, in the Ohio county two fifths of the families had incomes under $1,000 Although in the country as a whole per capita incomes were more than twice as high in 1948 as in 1940 food prices also about doubled in that period Food costs affect everyone whereas not all families have shared equally in income advances Consequently large numbers cannot afford to buy the kinds and quantities of foods needed for good diets

Food for 4 persons in quantities and types included in the city worker s family budget developed by the Bureau of Labor Statistics would have cost about $20 a week in June 1947 in the 34 cities in which the budget was priced This budget represents a modest but fairly adequate standard of living The kinds and quantities of food included are typical of those purchased by American families whose diets provide approximately the dietary allowances recommended by the Food and Nutrition Board of the National Research Council

The trend in food prices is shown by the following figures To follow a low cost food plan prepared by the Bureau of Human Nutrition and Home Economics, a family of 4 might have spent at average city prices

June 1936	$ 9 00-$10 00
June 1942	10 00- 11 00
June 194	13 00- 14 00
June 1948	18 00- 20 00

In 1948 it would have taken about 50 per cent of a $2 000 family income to provide this diet and 35 per cent in 1945 Figures are not available to show how many 4 person families earned $2 000 or less in 1948 In 1945 it was estimated that about one fourth of the 4 person families in the United States had incomes under $2 000 Food costs for larger families are proportionately higher of course Of the total number of families of 5 or more persons, 30 per cent had incomes under $2 000 in 1945

Even for small families food costs are frequently a problem A fifth of the 2 person families had incomes under $1 000 in 1945 Expenditures for this low cost

adequate diet would have amounted to $10 or $11 a week in June 1947, or about 55 per cent of the weekly share of an income of $1 000 for the year

Even with the income increases that took place in 1947 and 1948, it is likely that thousands of families are

TABLE 1—*Calculated Nutritive Value of U S Civilian per Capita Food Supply Prewar 1945 and 1948 Compared with Recommended Dietary Allowances (1948) of the National Research Council's Food and Nutrition Board*

Nutrient		Nutritive Value per Capita per Day*			Per Capita Allowances Based on Recommendations of the National Research Council†
		1935-1939	1945	1948	
Food energy	cal.	3,[illegible]0	3,3[illegible]0	3 530	2 600
Protein	Gm	89	103	96	65
Calcium	Gm	0.90	1 08	1 06	1 06
Iron	mg	13.8	19 0	17.5	11 6
Vitamin A value ‡	I U	8 100	9 800	8 [illegible]00	4,560
Thiamine total	mg	1 54	2 [illegible]4	2 09	1 24
Thiamine per 1 000 calories	mg	0 47	0 66	0 63	0 48
Riboflavin	mg	1.86	2 55	2 38	1 63
Niacin	mg	15 4	21 9	19 9	1[illegible]4
Ascorbic acid	mg	115	139	1[illegible]7	[illegible]0

Computed by the Bureau of Human Nutrition and Home Economics on basis of estimates prepared by the Bureau of Agricultural Economics of apparent civilian consumption (retail basis) including foods supplied by farm and city gardens. No deductions have been made for waste of food in the home or for losses of nutrients in food preparation No allowance has been made for nutrients added to the food supply through the use of baking powder yeast mold inhibitors the added minerals in self rising flour or for nutrients added in the processing of certain foods such as vitamins used as antioxidants and calcium salts used in some canned foods

† Recommended dietary allowances suggested for 17 sex age-activity groups (National Research Council Reprint and Circular Series no 129 Revised 1948) were weighted by the number of persons in each group according to 1948 population estimates

‡ Vitamin A values expressed as international units include carotene sources Carotene was converted on the basis that 0 6 microgram of beta-carotene or 1.2 micrograms of other vitamin A active carotenoids is equivalent to one I U of vitamin A Current research suggests that many of the vitamin A values ascribed to carotene-rich foods in the literature need to be revised and as they stand probably are too high to indicate physiologic utilization Hence the calculations in this table may considerably overestimate the margin above recommended allowances

spending a relatively large share of the family income for food at the expense of other needs and that unless they spend this money for food in a nutrition-wise fashion and so handle and prepare the food as to conserve food values to the utmost, diets are deteriorating accordingly

The relation of income to food consumption has been shown by many dietary studies This relationship is most clearly shown by data from a fairly homogeneous sample—that is, from families of similar composition living in the same kind of community in the same region Some of the most recent dietary studies were made during the war years when food rationing influ enced normal consumption patterns and obscured some what the full effects of income Hence the data selected to show the relation of income to diet in table 2 are from a nationwide study in 1935 1936, they show

TABLE 2—*Consumption in a Week by Families of Husband and Wife and 1 or 2 Children Under 16 in New England Middle Atlantic and North Central Villages 1935 1936* *

Income Class (Dollars)	Families No	Milk Equivalent † Qt	Eggs Doz	Meat Poultry Fish Lb	Fats ‡ Lb	Flour Equivalent § Lb	Dry Beans and Peas Lb	Potatoes Sweet Potatoes Lb	Fresh Vegetables Lb	Fresh Fruit Lb
0-499	9	10 7	1 3	4 9	2 7	10.3	0 9	16 2	4 1	6 4
500-999	108	10.2	1.5	6 4	2 9	10 0	0.5	12 6	4 5	6.4
1 000-1 499	171	12.3	1 7	8 0	3.0	10 0	0 4	12 5	5 8	8.2
1 500-1 999	83	13 4	1 7	9 6	3 0	9 9	0 3	11 0	7.6	11 0
2 000-2 999	51	15 8	1.9	9 9	3 1	11 0	0 2	11 0	7 9	12 6
3 000-4,999	12	15 7	1 5	10 9	3.3	9.3	0 6	12 5	8 6	12.2

Stiebeling H K Monroe D Phipard E F Adelson S F and Clark F Family Food Consumption and Dietary Levels Five Regions *Miscellaneous Publication 4 United States Department of Agriculture* 1941

† Approximately the quantity of fluid milk to which the various dairy products (except butter) are equivalent in minerals and protein.

‡ Includes butter bacon and salt pork

§ Two thirds of the weight of baked goods has been added to that of flour meals and cereals

weekly consumption of selected foods by families of husband and wife and 1 or 2 children under 16 living in villages of the New England Middle Atlantic and North Central regions

In successively higher income classes these families used larger quantities of milk, meat, fresh vegetables and fresh fruit Consumption of eggs and fats increased slightly and that of grain products (in terms of flour equivalent) changed little while quantities of dried peas and beans and of potatoes declined

Family Size—The kind of diet a family can have depends not only on family income but on the number of persons that income must support Within a given

income class, total expenditures for food increase with increasing family size but food expenditures per person decrease The figures in table 3 show food expenditures in September October 1944 of city families with incomes for the year between $2 000 and $3 000 [2]

While there may be some economy in buying food in larger quantity it is relatively small compared with the added cost of feeding more persons The result *is that diets of large families tend to contain smaller* quantities of protective foods and, therefore, are less likely to be adequate nutritionally than diets of small families at the same income level.

Additional data on the relation of family size to the character of the diet are given below These figures

TABLE 3—*Food Expenditures of City Families with Annual Incomes of $2,000 to $3,000 (September October 1944)*

Number of Persons in Family	Average Food Expense in 1 Week	
	Per Family	Per Person
1.	$9 6	$9 6
2.	14 42	7.21
3.	16.53	5.[illegible]1
4	18.[illegible]8	4.64
5	[illegible]0.55	4.11
6 or more	24.51	4.08 or less

show the estimated expenditures in October 1947 for meat poultry fats and eggs by families of different size living in Cumberland Md [3]

It is apparent that the larger the household size the smaller was the average expenditure per person for meat poultry eggs and fats The average amounts spent in households of 2 persons would have been almost enough to purchase the quantities of these foods *suggested in the moderate cost food plan of the Bureau* of Human Nutrition and Home Economics At October 1947 prices an expenditure of from $3 30 to $3 60 per person would have been needed to buy these quantities for a household of a moderately active man and woman. However, fewer than half the 2 person families in Cumberland were spending more than $3 per person

2 Wartim Food Pu cha s Bulletin 838 Un ted States Department of Labor 1945

3. Bureau of Human Nutrition and Home Economics Unpublished data.

a third were spending less than $2 for which they scarcely could have purchased the quantities of these foods in the low cost food plan

In the 4 person household average expenditures per capita were close to the estimates of the cost ($2 50 to $2 70) of meat poultry, eggs and fats in the moderate cost plan for 2 moderately active adults, a boy 13 to 15 and a child 7 to 9 years of age Only 40 per cent of the 4 person Cumberland families were spending this amount or more

In the 7 person households average expenditures for meats eggs and fats were only $1 32 per person per week This is less than the amount needed in October

TABLE 4—*Relation of Family Size to Diet (October 1947 Cumberland Md)*

Household Size	Average Expenditure per Person per Week for Meat, Poultry Eggs Fats	Percentage of Families Whose Expenditures per Person for Meat Poultry Eggs and Fats Were in Excess of		
		$2 00	$[illegible]0	$3 00
2 or less	$3 [illegible]0	64	55	46
3	2 [illegible]9	0	35	25
4	2 [illegible]8	53	42	28
5	1 64	33	17	17
6	1 [illegible]9	11	11	
7 or more	1.32	13	4	

1947 ($1 45 to $1 60) to buy these foods in the low cost diet of the Bureau of Human Nutrition and Home Economics for a family of 2 adults, 2 teen age and 3 younger children

Differences between the low cost and the moderate cost food plans [4] are illustrated by the weekly quantities of foods suggested for the family of 4 previously described (table 5)

Season—Few studies have been made to show seasonal differences in the nutritive content of family diets There is evidence that considerable variation may be found in part associated with seasonal availability of food supplies For example consumption of sweet pota toes in the South is highest in the months following

4 Based on September 1948 food plans The following publications on food plans may be obtained from the Bureau of Human Nutrition and Home Economics United States Department of Agriculture AIS 21 Food for Two AIS 59 Food for the Family with Young Children AIS 71 Food for the Family with School Children and Miscellaneous Publication 662 Helping Families Plan Food Budgets

their harvest and decreases in late winter as stored supplies diminish This seasonal change in consumption influences the vitamin A value of diets In towns and cities, abundant market supplies of fresh citrus fruit at reasonable prices may tend favorably to influence the ascorbic acid content of diets during late winter and spring

Some seasonal variations may be the result of changes in the foods themselves In general, vitamin values of foods tend to decrease during prolonged storage Potatoes stored six months may have lost two thirds of the ascorbic acid present at harvest Because they are eaten

TABLE 5—*Suggested Foods for Family of Four* *

	Low Cost Plan	Moderate Cost Plan
Leafy green and yellow vegetables	9 lb 4 oz.	13 lb 4 oz.
Citrus fruit tomatoes	9 lb 0 oz.	11 lb 0 oz.
Potatoes sweet potatoes	13 lb 8 oz	11 lb 0 oz.
Other vegetables fruit	7 lb 8 oz.	13 lb 8 oz.
Milk (or its equivalent)†	22 qt.	23½ qt
Meat poultry fish	7 lb 8 oz.	10 lb 8 oz.
Eggs	20 (eggs)	28 (eggs)
Dry beans and peas nuts	1 lb 6 oz.	12 oz.
Flour cereals ‡	14 lb 4 oz.	12 lb 4 oz
Fats and oils §	3 lb 4 oz	3 lb 10 oz.
Sugar sirups preserves	3 lb 4 oz.	3 lb 14 oz.

* Two adults a boy 13 to 15 years and a child 7 to 9 years
† In cheese cream ice cream
‡ Count 1⅓ pounds (650 Gm) of bread or baked goods as 1 pound (454 Gm) of flour
§ Includes butter bacon salt pork.

in fairly large quantities potatoes constitute an important potential source of ascorbic acid However their contribution toward the end of their season may be much less than at the beginning Farm families dependent for vitamin C on home-grown and stored potatoes cabbage apples and canned tomatoes and other vegetables may be running low in this nutrient along toward spring Studies of ascorbic acid levels in plasma of school children in rural areas have shown this to be the case

Availability—It is usually taken for granted in the United States that if people have enough money they can buy the foods needed for a good diet Yet this is not always true In some sections of this country the local supply of milk has been inadequate for school feeding programs Other examples could be cited to

show how differences in availability of food supplies from one place to another may affect food consumption and the nutritional quality of the diet

Food Habits—Poor diets are often the result of poor food habits even when there is enough money for food At almost any level of expenditure above a certain minimum, some families manage to have nutritionally good diets while others do not For example, the figures below show the proportion of families with different kinds of diets obtained for about the same amount of money These were village and city families in the North and West with food expenditures in 1936 between $2 77 and $3 45 per food expenditure unit per week The proportions are as follows

Good diet	24%
Fair diet	64%
Poor diet	12%

Reports of poor food habits have been numerous in the last two or three years Sometimes conclusions are based on the number of servings of different types of food in a day or a week as compared with some arbitrary meal pattern In other studies conclusions relate to calculations of the nutritive value of the food consumed during a given period

A recent analysis of some 25 000 one day food records throws light on current food habits in four areas studied by the United States Public Health Service under their Nutritional Appraisal and Demonstration Program These food records were obtained from persons a large proportion of whom were children, being examined for physical evidence of nutritional deficiency In one area 59 per cent of the subjects reported no green or yellow vegetables during the day of the record, in one area 61 per cent reported no milk or less than 1 cup and in one area about three fourths had no vitamin C rich food, such as citrus fruit tomatoes or raw green cab bage The types of foods which seemed least likely to be missing during a day were enriched grain products and such foods as meats or eggs

These data were considered indicative of food habits which if continued over a long period may result in measurable evidence of nutritional deficiencies Clin ical observations among the persons studied bore this out Signs and symptoms suggestive of mild deficien cies were common although severe malnutrition was

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Good diet	21
Fair diet	6[illegible]
Poor diet	1[illegible]

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Research has shown that delays in marketing and improper or prolonged storage as well as processing methods take their toll of some of the vitamins Further losses in nutrients occur in the kitchen Some of these are needlessly large because of poor food preparation practices the holding or reheating of cooked products and the waste of edible food In addition the nutritive content of foods may be increased to some extent through improved animal feeding and breeding plant breeding and better cultural practices

School Lunches — Among the fruitful efforts to raise nutritional levels are those concerned with the improved feeding of children. One good school meal a day can do much toward improving the well being of children whose home diets are not providing adequately for food needs Numerous observations on the attendance behavior and progress of children receiving school lunches would seem to bear this out As a result school lunch programs have been widely endorsed in the United States as in other countries by health officers nutritionists and others concerned with promoting higher levels of nutritional health

Several studies have been planned to measure objectively the nutritional benefits to children participating in school lunch programs One of these[6] carried on over a five year period among rural children in Florida provides evidence that the school lunch offers an effective means of raising the nutritional status of school children The authors however stress the importance of adequate supervision and special planning to take care of known deficiencies Lack of these controls may explain in part why some studies have not shown such clearcut results

Perhaps almost as important as the food itself is the educational experience provided by the school lunch. Eating well planned well cooked meals day after day cannot fail to be influential in establishing good food habits This experience will be most effective if accompanied with an integrated program of nutrition education throughout the curriculum

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6 Abbott, O D Townsend, R. O French, R B., and Ahmann, C. F Effectiveness of the School Lunch in Improving the Nutritional Status of School Children, Bulletin 426 University of Florida, Agricultural Experiment Station, 1946

addition of iodine to salt, vitamin A to margarine and the restoration of some of the nutrients lost in the milling of cereal products

Enrichment of flour and bread with iron, thiamine, riboflavin and niacin was endorsed by the Food and Nutrition Board of the National Research Council and by the Council on Foods of the American Medical Association as a means of safeguarding health and well being, especially during the war period It began on a voluntary basis in 1941 but by the end of the second year about three fourths of all family flour and bakers' white bread was enriched Under War Food Order No 1, enrichment of bakers' white bread was made mandatory from January 1943 to October 1946 As of November 1948, twenty-three states and two territories Puerto Rico and Hawaii had enacted legislation requiring enrichment of both bread and white flour sold within their boundaries In the remaining states, voluntary enrichment is being continued extensively according to recent surveys made by the industry

Because bread and flour are consumed in relatively large quantities and by almost everyone enrichment of these foods had a measurable effect on the nutritive value of the average diet as pointed out earlier According to calculated values the per capita food supply in 1945 provided 17 per cent more iron 27 per cent more thiamine 12 per cent more riboflavin and 19 per cent more niacin than it would have without enrichment of these foods In individual diets benefits were proportional to the consumption of bread and flour Presumably they would be greater among the low than the high income groups

Enrichment of degerminated cornmeal and grits was a logical sequence to the flour and bread program since these foods are used so extensively in certain areas of the country Several of the Southern states have passed laws requiring enrichment of these products at levels promulgated by the Federal Food and Drug Administration

Another practical field of endeavor and one economical of our resources is the fuller conservation of nutrients originally present in foods The milling of grains to retain a high proportion of their original food value is an example of what might be accomplished

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[6] Abbott O D Townsend R O French R B and Ahmann C F Effectiveness of the School Lunch in Improving the Nutritional Status of School Children Bulletin 426 University of Florida, Agricultural Experiment Station 1946

The present federal school lunch program operates under the National School Lunch Act, which was passed in 1946 In the school year ending June 1948 nearly 45,000 schools participated in the indemnity plan which means that sponsors were reimbursed by the govern ment for part of the local purchases of food provided that the meals served met certain specifications In the peak months more than 6,000 000 children had a school lunch with the peaks maintained longer than in 1947 Indications are that as the states work out better provisions for administering the program it will expand and go forward on a more stable and permanent basis

In addition to the federal assistance given by reim bursement in the indemnity plan, the Department of Agriculture makes available for use in the lunch program special purchases of certain foods These foods provide an important nutritional contribution to the meals served Purchases for the year 1947-1948 included such foods as nonfat dry milk, cheese dried eggs, dried fruits peanut butter, sweet potatoes and concentrated orange juice

The school lunch program provides one means for more equitable distribution of national food supplies in accordance with need If expanded to include all children in school it would go far to safeguard the nutritional health of this group Less attention has been given in the United States to meeting the special food needs of expectant and nursing mothers infants and preschool children In some countries these groups are given high priority in the distribution of available foods

Home-Produced Food—Food raised for family con sumption not only spares cash for other needs but improves the family diet as well The kinds of foods that are home produced on many farms—milk, eggs meats vegetables and fruit—are good sources of the nutrients likely to be low in diets of many families Even the city backyard garden is worth while, families who raise their own vegetables tend to eat more At the same time they are taking advantage of freshly harvested products thereby avoiding the nutrient losses often incurred in usual marketing procedures For many families more extensive or better planned home production offers the most feasible way of improving diets

Education —The importance of education as a factor in raising nutritional levels cannot be overemphasized Every one needs to know how to select an adequate diet The lower the income the more difficult it becomes and the more important it is that the food dollar be spent to best advantage. However many persons who can afford good diets do not know enough about food selection

Knowledge of nutritional requirements and how they may be met by foods while far from complete, has advanced far enough to offer sound guidance in our teaching But the application of the knowledge we have has lagged behind its development Nutrition education in a broad sense includes convincing people that what they eat makes a difference Experience has shown that motivation is the most difficult hurdle to surmount in trying to change food habits It is essential that the physician nurse nutritionist teacher and other key persons in the community have a strong personal conviction of the importance of the right food for the growth and development of children and for optimal health and well being at all ages For this they also need scientific information about food values in relation to cost in order to understand the practical aspects of feeding problems While an able job in nutrition education is being done on many fronts more widespread and more adequate education in all aspects of the nutrition problem is needed by every one from health officers and other physicians down to the food manager for the family and the individual consumer Determining the ultimate success in the broad practice of nutrition and holding the key to the adequacy of American diets is the housewife who spends the family food money who prepares the family s three meals a day and who guides the food habits of children in their formative years The physician as one of the influential members of society must give his support to this aspect of training for homemaking

CHAPTER XXV

FOODS OF PLANT ORIGIN

LEONARD A MAYNARD
and
WALTER L NELSON

Over 50 per cent of the American diet consists of foods of plant origin Indirectly as foods for animals plant products make an additional contribution to the human diet through their influence on the nutritive value of animal products

In discussing nutritive values it is necessary to make use of certain average figures for nutrient composition Foods of plant origin are subject to rather wide variations in composition as influenced by genetic soil and climatic factors It is beyond the scope of this article to consider these factors Their importance is illustrated by the reports of a number of investigators[1] Some of the factors influencing mineral composition have been reviewed by Beeson[2] Fortunately the consumer seldom gets his supply of a given food from a single agricultural source and thus the significance of the wide variation in the composition of crops differently produced is not nearly so great as the individual values might suggest There are also variations in foods as consumed caused by processing storage and cooking factors In the present article attention is called to these factors if they have a particular bearing on the significance of the average values cited For convenience of discussion the foods of plant origin are grouped as follows cereals legumes and nuts potatoes other root crops tomatoes leafy vegetables miscellaneous vegetables fruits sugar syrups and molasses and vegetable oils

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1 Chatfield C and Adam G Food Compo it on in Food and Life Yea book f Ag icultur Wa b ngton D C Government P nt ng Office 1939 p 7 Hamner K C and Mayna d L A Fa tors I fluencing the Nutr t v Value of the Tomato Miscell neous Publ cat ons 50 Un ted States Dep rtment of Agriculture 194 S ott, G C and Belkengren R O Importan e of B ed ng Pea and Corn for Nutritional Qual ty Food Re earch 9 371 (S pt Oct) 1944

2 Beeson K C Th Mi eral Compo t on of Cr ps w th Pa t cular R ference to the S l n Which They A e Grown M scellaneous Bulletin 369 Un ted States Departm nt of Ag cult re Ma ch 1941

CEREALS

Under cereals are included the cereal grains and their products, including flour, bread breakfast foods crackers, cookies, pastry and macaroni Because of the low cost of cereals in relation to most other foods, their consumption is largest among the low income groups The importance of these foods in the diet has been set forth editorially in THE JOURNAL[3] as follows

> The cereal grains are the backbone of the nutrition of most of the races of the earth They are, as a rule the cheapest sources of food fuel so that corn wheat, rice rye barley and oat kernels are to be found constituting a thi d or often much more of the calory intake of the millions of persons involved

Cereals also provide a third or more of the protein of the American diet While this protein is not so high in biologic value as that of animal products, combi nations of cereal and animal protein provide a diet of

TABLE 1—*Proximate Composition of Whole Wheat and of White Flour*

	Protein Percentage	Fat Percentage	Carbo-hydrates Percentage	Crude Fiber Percentage
Wheat flour graham	13 0	2 0	72 4	1.8
Wheat flour patent	10.8	0 9	75 9	0 3

excellent protein quality Important amounts of phos phorus, iron copper and other minerals and of certain vitamins are supplied by cereals Generalizations here are of limited value however, because of the differences among cereals and the losses which result from milling

Wheat—Wheat is by far the leading cereal in the diet in the United States furnishing approximately 25 per cent of the total calories consumed The total per capita consumption of flour for 1945 is estimated at 164 pounds (74 Kg) 97 per cent of which was the *milled product leaving less than 5 pounds (2 Kg)* as whole wheat or graham flour The consumption of wheat breakfast foods approximated 1½ pounds (0 7 Kg) per capita The proximate composition of the flours as listed by Chatfield and Adams[4] is presented in table 1

3 The Cereals in Nutrition editor al J A M A 95 1101 (Oct. 11) 1930

4 Chatfield C and Adams Prox mate Composition of American Food Material C rcular 549 United States Department of Agr culture June 1940

It is clear that wheat makes a substantial contribution to the protein needs of the diet Using the percentage figure for patent flour, one may calculate that the average daily consumption of 6 8 ounces (225 Gm) of flour supplies 22 Gm of protein daily, or nearly one third the daily allowance Whole wheat contains more protein than white flour, and its protein has a higher biologic value, but when white flour is supplemented with milk eggs or meat a protein mixture of high biologic value results The much lower fiber content of patent flour reflects the removal of the bran in milling While bran contributes laxative qualities to the diet it is poorly digested and may be somewhat irritating to the mucous membranes of the digestive tract The physiologic effects of bran have been

TABLE 2—*Vitamin and Mineral Content of Flours*

	Whole Wheat Flour Mg /Lb	White Flour Mg /Lb	Enriched Flour Mg /Lb
Thiamine	2.63	0.30	2 0
Riboflavin	0.-6	0 15	1 2
Niacin	25.30	3.50	16 0
Iron	17.3	3.0	
Pantothenic acid	6 03	2 59	
Pyridoxine	09	0 90	

Minimum enrichment levels

reviewed by the Council on Foods and Nutrition[5] Several reports[6] have indicated that the calcium phos phorus and iron of whole wheat flour are poorly utilized and therefore the higher concentration of these nutrients in the whole wheat flours are for the most part an apparent and not a real benefit

In table 2 are presented the vitamin and mineral values of whole wheat and white flour and for com parative purposes the enrichment levels of white patent flour These levels are based on recommendations of the National Research Council and were compulsory under War Food Order No 1 of the Federal Security

5 The Nutritional Significance of Bran report of the Council on Foods J A M A. **107**:874 (Sept 12) 1936

6 McCance R A and Widdows n F M Mineral Metabolism of Healthy Adults on White and Brown Bread Dietaries J Physiol **101** 44 (Jun) 194- Pringle W J S and Moran T Phytic Acid and Its Destruction in Baking J Soc Chem Indust **61** 108 194 Widdowson E and McCance R A Iron Exchanges of Adults on White and Brown Bread Diet Lancet **1**:588 (May 16) 194-

Administration until Oct 25, 1946 At present (1947) these levels are required by legislation in nineteen states and Puerto Rico and Hawaii The values for thiamine riboflavin, niacin and iron are taken from Tables of Food Composition[7] Those for pantothenic acid and pyridoxine were supplied by Elvehjem[8]

The large milling losses of vitamins and minerals are evident from this table The data show that the outstanding superiority of enriched flour over ordinary white flour lies in its sixfold increase in thiamine content, the figure being 75 per cent of that for whole wheat flour The data show that milling results in a 60 per cent loss of pantothenic acid and a 50 per cent loss of pyridoxine Much of the phosphorus and certain other minerals are also lost

The enriched flour now on the market is nearly all produced by adding the nutrients in question to the refined product A somewhat similar product can be achieved by "longer extraction" in milling that is by retaining some of the vitamin and mineral rich portions of the wheat which are milled out in making patent flour This is the procedure officially adopted in Canada as described by Newman[9]

Wheat flour is consumed to a large extent in the form of bread, of which 85 per cent is commercially baked Most of this bread is made from white flour but it is estimated that a majority of the bread now consumed is the enriched product This enriched bread is obtained either by the use of enriched flour or by the direct addition of the specified minerals and vitamins to the dough

An important factor in the nutritive value of bread is the extent to which nonfat dry milk solids are used in its manufacture Six per cent of these is frequently mentioned as the desirable amount in modern bread but apparently much bread is made with 3 per cent or even less when the cost of nonfat dry milk solids is high Whole wheat bread is commonly made without milk solids The inclusion of 6 per cent of the solids increases the calcium content of white bread four

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7 Tables of Food Composition Miscellaneous Publication 572 United States Department of Agriculture 1945

8 Teply L J Strong, F M and Elvehjem C A Nicotinic Acid Pantothenic Acid and Pyridoxine in Wheat and Wheat Products J Nutrition 24:167 194

9 Newman L H The Retention of B Vitamins in Flour and Bread J Am Soc Agronomy 34 109 (Feb) 1942

times and the phosphorus content twice and adds 0 06 mg of thiamine and 0 36 mg of riboflavin per pound It also improves the protein value considerably Several reports[10] have appeared showing the improvement in the protein value of white bread made with milk solids when 3 to 5 per cent of soybean flour or 1 to 3 per cent of a cultured food yeast replaced a corresponding amount of the wheat flour used in baking

The proposed minimum standards for enriched bread which are now being followed are per pound thiamine 1 1 mg riboflavin 0 7 mg niacin 10 mg and iron 8 mg A similar content of nonfat dry milk solids being assumed, the thiamine content is approximately three times as large as that of ordinary bread the iron content is increased four times and the niacin content three times In other nutrients the enriched product falls somewhat short of whole wheat bread

Since whole wheat bread contains the bran which is largely absent in white or in enriched bread the question of relative digestibility is an important one This question was thoroughly studied by Rubner[11] during World War I He found that the advantage of the higher protein content of the unmilled product was offset by its lower digestibility and that it contained slightly less total available calories Noteworthy modern studies have been published by Murlin and his associates[12] The first study shows that whole wheat bread has in general a lower protein digestibility value but a higher protein biologic value The second study reveals no significant differences in the digestibility of the carbohydrates of the two breads The authors point out that any differences in protein or in available energy values are small and of little importance as compared with differences in vitamins and minerals

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10 Harris R S Clark M and Lockhart E E Nutritional Value of Bread Containing Soy Flour and Milk Solids Arch Biochem 4 243 (May) 1944 Volz F Forbes R. M Nelson W L and Loosli J K The Effect of Soy Flour on the Nutritive Value of the Protein of White Bread, J Nutrition **29** 69 (April) 1945 Sure B Nutritional Improvement of Cereal Flours and Cereal Grains J Am Dietet A. **22** 494 (June) 1946

11 Rubner M Die Verdaulichkeit von Weizerbrot Arch f Anat u. Physiol 1916 p 61

12 Murlin J R Marshall M E and Kochakian C D Digestibility and Biological Value of Whole Wheat Breads as Compared with White Bread J Nutrition **22** 573 (Dec) 1941 Sealock R R. Basinski D H and Murlin J R. Apparent Digestibility of Carbohydrates Fats and Indigestible Residue in Whole Wheat and White Breads ibid **22**:589 (Dec) 1941

Corn—Corn meal is the chief form in which corn is used as human food representing a per capita consumption of 23.4 pounds (11 Kg) in 1939. An additional 8 pounds (4 Kg) is consumed as breakfast foods, grits, hominy and canned corn.

The corn grain is approximately equal to the wheat grain in thiamine content but contains only one fourth as much niacin. It is a good source of phosphorus and iron and certain other minerals. But much of the corn meal and flour consumed as well as the hominy, grits and breakfast foods is in the form of milled products. The milling process removes the germ and the bran and thus takes out most of the thiamine and minerals present in the entire kernel. The Food and Drug Administration[13] however has set standards for enriched corn meal and grits entering interstate commerce which require that each pound contain not less than 2.0 mg and not more than 3.0 mg of thiamine, not less than 1.2 mg and not more than 1.8 mg of riboflavin, not less than 16 mg and not more than 24 mg of niacin or niacinamide and not less than 13 and not more than 26 mg of iron. North Carolina, South Carolina, Georgia, Alabama and Mississippi have compulsory legislation (1947) which requires that all degermed corn meal and grits sold in the state meet these requirements. These products contain 8 to 9 per cent of protein which ranks below wheat in biologic value but which combines with milk *to provide a protein mixture of high quality.* Elvehjem[14] has recently reviewed the role of corn in pellagra-producing diets. The special reason for enriching corn with niacin is based on the fact that this cereal is used by certain groups in diets which as a whole are low in protein and specifically the amino acid tryptophan. Niacin can serve to *decrease the* requirement for tryptophan. Inasmuch as corn is low *in both tryptophan and niacin it is evident* that more niacin is required. Yellow corn meal differs from the white variety as well as from other cereals in containing a significant amount of vitamin A, 350 to 500 international units per hundred grams. In view of the rather large consumption of corn meal and other milled

13 Enriched Corn Meal and Grits, Food and Drug Administration, Federal Register, May 7, 194 , p 311.

14 Elvehjem, C. A. Corn and Pellagra in Conference on Corn Enrichment, Clemson, S. C. Clemson Agricultural College, July 1947

corn products by certain groups of the population the wider use of the unmilled or enriched meal or the development of milling methods which would retain nutrients now lost would be highly desirable

Canned corn is equal to corn meal in energy and protein on an equivalent moisture basis and is superior to the milled product in mineral and thiamine content

Oats—Among the breakfast food cereals, oatmeal and rolled oats the principal forms in which oats are consumed rank first both in quantity eaten and in nutritive value Approximately 529 million pounds (240 million Kg) are consumed annually In the milling of oats only the fibrous hull and the adhering portions are removed the germ and the other vitamin-rich and mineral rich portions being left with the product used for human food Thus oatmeal ranks nutritionally as a whole grain cereal rather than as a milled product

Oat cereals rank above wheat products both in fuel value and in protein content Their higher fuel value is due primarily to their fat content (7 4 per cent) Their protein content over 14 per cent outranks that of white wheat flour in biologic value Both oatmeal and rolled oats are low in crude fiber and when properly cooked are highly digestible

Oatmeal is considerably richer than whole wheat in thiamine Aughey and Daniel [15] reported that one hundred and twenty minutes cooking in a double boiler did not cause any appreciable loss of thiamine from rolled oats The following values for the various vitamins have been reported [7] for uncooked oatmeal thiamine 2 5 mg per pound riboflavin 0 63 mg per pound and niacin 5 0 mg per pound

Oatmeal is a rich source of iron (23 4 mg per pound) Its phosphorus content 66 per cent of which is in the form of phytin is similar to that of whole wheat

Rice—Rice supplies slightly more than 1 per cent of the calories of the average American diet the annual per capita consumption being approximately 5 pounds (2 Kg) White or milled rice the form in which most of the consumption occurs is essentially an energy food The protein content is around 7 5 per cent thus being

15 Aughey E and Daniel E P Effect of Cooking on the Thiamine Content of Foods J Nutrition 19 285 (March) 1940

Corn —Corn meal is the chief form in which corn is used as human food representing a per capita consumption of 23 4 pounds (11 Kg) in 1939 An additional 8 pounds (4 Kg) is consumed as breakfast foods grits hominy and canned corn

The corn grain is approximately equal to the wheat grain in thiamine content but contains only one fourth as much niacin It is a good source of phosphorus and iron and certain other minerals But much of the corn meal and flour consumed as well as the hominy grits and breakfast foods, is in the form of milled products The milling process removes the germ and the bran and thus takes out most of the thiamine and minerals present in the entire kernel. The Food and Drug Administration [13] however has set standards for enriched corn meal and grits entering interstate commerce which require that each pound contain not less than 2 0 mg and not more than 3 0 mg of thiamine not less than 1.2 mg and not more than 1.8 mg of riboflavin not less than 16 mg and not more than 24 mg of niacin or niacinamide and not less than 13 and not more than 26 mg of iron. North Carolina South Carolina Georgia, Alabama and Mississippi have compulsory legislation (1947) which requires that all degermed corn meal and grits sold in the state meet these requirements These products contain 8 to 9 per cent of protein which ranks below wheat in biologic value but which combines with milk to provide a protein mixture of high quality Elvehjem [14] has recently reviewed the role of corn in pellagra-producing diets The special reason for enriching corn with niacin is based on the fact that this cereal is used by certain groups in diets which as a whole, are low in protein and specifically the amino acid tryptophan. Niacin can serve to decrease the requirement for tryptophan. Inasmuch as corn is low in both tryptophan and niacin it is evident that more niacin is required. Yellow corn meal differs from the white variety as well as from other cereals in containing a significant amount of vitamin A 350 to 500 international units per hundred grams In view of the rather large consumption of corn meal and other milled

13 Enriched Corn Meal and Grits, Food and Drug Administration, Federal Register May 7 1947 p 3112.
14 Elvehjem, C. A. Corn and Pellagra, in Conference on Corn Enrichment, Clemson, S. C., Clemson Agricultural College, July 1947

LEGUMES AND NUTS

Dry legume seeds, such as beans, peas and lentils, are approximately twice as rich in protein as the cereals. While most legume proteins are of rather low biologic value when fed alone, their deficiencies are made up by other proteins in a mixed diet. Dried beans, either home cooked or canned, are noteworthy as a cheap source of protein even though the digestibility is somewhat less than for protein from many other sources.

Dried navy and kidney beans, green or dried lima beans, green or dried peas, lentils and cow peas are all rich sources of thiamine, containing around 0.5 mg per hundred grams of the dried seed. A part of this thiamine is lost, however, in the cooking process. Two thirds of a cup of baked canned beans should nevertheless supply one eighth of the day's thiamine requirement. These legumes also supply significant amounts of riboflavin. Fresh green lima beans and peas are rich in ascorbic acid, but a large loss is involved in cooking. The legume seeds are noteworthy also for their iron content, the dried products containing from 6 to 10 mg per hundred grams. Two thirds of a cup of baked beans will supply one half the daily adult allowance. Legume seeds are notably higher in calcium and in phosphorus than are even the whole cereal seeds.

It is evident that a larger consumption of dried legumes, particularly in place of refined cereals, would improve the diet in several respects. Their cheapness commends them especially for use in low cost diets.

Green and yellow string and wax beans, classed as seed pods, are comparable to the legume seeds in protein, minerals and thiamine per unit of dry matter and in addition contain notable amounts of vitamin A, riboflavin and ascorbic acid.

Peanuts have nutritive values similar to those of the other legumes. They have a much higher energy value due to the high fat content (44 per cent) and the protein is of high biologic value. Peanut butter has a nutritive value similar to that of peanuts. Soybeans are nutritionally similar to peanuts. They are little used as human food in this country. Walnuts are comparable to peanuts in thiamine content, but almonds have somewhat less. All have a high fat and a high protein content and are comparable as sources of calcium and phosphorus.

lower than that of corn Over 50 per cent of the minerals and 85 per cent of the thiamine of the entire kernel are lost in milling In contrast brown rice the product that results when only the hull is removed, contains 0 7 to 0 9 mg of thiamine per hundred grams It is nutritionally superior in other respects also A change from white to lightly milled rice would certainly be in the interests of better nutrition

Recent developments in the nutritional improvement of white rice have been described by Kik and Williams[16] Several processes have been proposed for the preparation of milled rice with improved retention of the various vitamins A comparison of white rice prepared by the conversion process with that of raw rice is given in table 3 It can be seen that a high percentage of the vitamins are retained in the milled product when the conversion process is used

TABLE 3—*Thiamine Riboflavin and Niacin Content of Rice*

Type of Rice	Thiamine Mg /Lb	Riboflavin, Mg /Lb	Niacin Mg /Lb
Rough (brown)	1 48	0 28	6 6
Converted (milled)	1 [illegible]6	0 [illegible]0	20 7
Raw (milled)	0 20	0 08	8.3

Rye—The consumption of rye mostly as milled rye flour in bread is less than 3 pounds (1 3 Kg) per capita annually This flour is similar to white wheat flour in energy and in protein content The whole grain contains approximately 2 1 mg of thiamine per pound 0 95 mg of riboflavin and 7 7 mg of niacin Although some of the vitamins are lost when rye flour is degerminated and bleached it is still a better source of most of the B complex factors than white wheat flour

Barley—A small amount of barley is consumed as pearl barley and as barley flour for infant feeding These are milled products which are apparently similar to white wheat flour in energy value but lower in protein content Milling removes minerals and vitamins to an extent similar to that in the case of wheat

16 Kik M C and Williams R. R. The Nutritional Improvement of White Rice Bulletin 112 National Research Council June 1945

The consumption of sweet potatoes in pounds is only about 25 per cent that of the white variety previously discussed. However, per unit weight it contributes appreciably more calories owing to the higher dry matter content of the sweet variety. Like the white, the sweet potato is primarily an energy food low in fiber and highly digestible. Only 6 per cent of the total calories are in the form of protein as compared with 10 per cent for the white variety.

Sweet potatoes are especially noteworthy, however, for their vitamin A value (7,700 international units per hundred grams[9]). Thus an average sized serving would supply more than the adult daily allowance of 5,000 international units.[18] Sweet potatoes are apparently similar to white in vitamin C content but lower in thiamine. They are also lower in iron and make no significant contribution to the diet as regards other minerals except possibly in certain trace elements. An excellent study of the nutritive value of dehydrated sweet potatoes has been published by Lease and Mitchell.[19]

Other Root Crops.—Among other root crops the carrot is high in carotene content. Converting the carotene into international units of vitamin A the values range from 2,200 to 10,000 units per hundred grams, so that approximately three fourths of a cup of cooked carrots should furnish one half to more than two times the daily adult allowance. However, there is some question as to how carotene from various sources is utilized by the body. Utilization values as low as 1 to 19 per cent for man have been reported in the literature.

Compared with the carrot on a caloric basis, turnips furnish similar amounts of thiamine, riboflavin, iron and protein, 50 per cent more calcium and eight times as much vitamin C. Swede juice has been reported one half as rich as orange juice. One half a cup of properly cooked turnips should supply approximately one fifth

18 In setting up this allowance, it was recognized that somewhat more would be required if all the units were furnished as carotene and somewhat less if all were furnished by vitamin A itself, because a unit in the form of carotene *may* be, under certain conditions at least, only about half as effective in human nutrition as a unit of vitamin A itself. Thus the rating here given for sweet potatoes, while accurate for comparison with other plant sources of *vitamin A*, overrates the vegetable in comparison with a source of vitamin A itself. The same considerations apply to later discussions of the vitamin A value of the foods included in this paper.

19 Lease, E. J., *and* Mitchell, J. H., Biochemical and Nutritional Studies of Dehydrated Sweet Potato, Bulletin 329, South Carolina Agricultural Experiment Station, June 1940.

VEGETABLES

Under the heading "vegetables" are grouped a great variety of foods which differ widely in their nutritive values

Potatoes—According to statistics of the United States Department of Agriculture, approximately 275,000 000 bushels of white or Irish potatoes are consumed in the United States per year or approximately 125 pounds (57 Kg) per capita Thus potatoes provide approximately 4 per cent of the total caloric needs on the average For many persons, however particularly the lower income groups potatoes make up a much larger part of the diet than this average figure indicates and their nutritive value is of added concern accordingly

Potatoes are primarily an energy food, consisting largely of starch Approximately 10 per cent of the total calories are in the form of protein of good biologic value The potato is low in fiber and according to various investigators it is highly digestible (92 to 99 per cent) It is a significant source of iron in that one medium-sized potato may provide as much as one tenth of the daily requirement

As harvested potatoes contain 12 to 35 mg of ascorbic acid per hundred grams and thus provide a substantial amount of this vitamin There is a continuous loss in storage however, which amounts to 50 to 70 per cent in twelve months The initial loss is rapid There is a further loss in cooking ranging from 14 to 66 per cent according to the procedure as reported by Esselen and co workers[17]

The thiamine content of the potato ranges from 95 to 165 micrograms per hundred grams which would mean from 8 to 14 per cent of the adult daily requirement in a 150 Gm serving (approximately the average daily consumption) if it were not for cooking losses The potato does not supply a significant amount of riboflavin Iron is richest in the outer portions of the potato vitamin C seems to be evenly distributed throughout There is evidence that the vitamin and mineral loss is less in potatoes boiled with the skins on than when baked but the loss is greatest for peeled potatoes

17 Esselen W B Lyons M E and Fellers C A The Composition and Nutritive Value of Potatoes with Special Emphasis on Vitamin C Bulletin 390 Massachusetts Agricultural Experiment Station March 1942

The consumption of sweet potatoes in pounds is only about 25 per cent that of the white variety previously discussed However per unit weight it contributes appreciably more calories owing to the higher dry matter content of the sweet variety Like the white the sweet potato is primarily an energy food low in fiber and highly digestible Only 6 per cent of the total calories are in the form of protein as compared with 10 per cent for the white variety

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19 Lease E J., and M tch ll J H B ochemical and Nutritional Studies of D hydrated Sweet Potat Bulletin 329 South Carolina Agricultural Experiment Station June 1940

the adult daily allowance of ascorbic acid Beets are similar to carrots as regards riboflavin and vitamin C content and contain more iron and protein Raw onions are also a good source of vitamin C[7] but storage losses range from 14 to 50 per cent and thus old onions are not a reliable source

Tomatoes —Tomatoes are important both because of their special nutritive values and because of their wide spread production They rank third in quantity among the vegetable crops being exceeded only by white and sweet potatoes Among the canned vegetables, the tomato in its various forms ranks first

Tomatoes are outstanding as a source of ascorbic acid having an average content of 25 mg per hundred grams for the summer grown products Thus one small tomato will supply about one third the recommended daily allowance for the adult (75 mg) The acidity of the tomato protects it against any considerable loss in cooking In the canning of tomatoes and tomato juice there is little loss of the vitamin if the process is prop erly carried out However tomato juice purchased on the retail market has been shown to vary considerably in ascorbic acid content Values ranging from 2 5 mg to 25 2 mg per hundred grams have been reported One 5 ounce (150 ml) glass of tomato juice supplies about one third the daily allowance Recent evidence indicates that tomatoes as purchased on the northern markets in winter contain much less ascorbic acid than those available in summer

Tomatoes are also rich in carotene Ripe tomatoes fresh or canned contain approximately 1 000 inter national units of vitamin A per hundred grams This means that one small tomato or a 5 ounce glass of canned juice will supply about one fifth the daily adult allowance

On the basis of the available figures tomatoes in the amounts consumed cannot be considered as an important source of any of the B group of vitamins or of the mineral elements with the possible exception of iron

Leafy Vegetables —The leafy vegetables including cabbage kale chard broccoli spinach turnip greens collards lettuce and beet greens are outstanding sources of certain minerals and vitamins They are particularly noteworthy for their calcium the important element in which cereals potatoes and most other foods except milk

and cheese are deficient. Among the leafy vegetables mentioned, turnip greens rank at the top in calcium content. One half cup (3 ounces or 90 ml.) of the cooked greens will supply approximately one third the daily adult allowance. Broccoli, collards, kale, loose leaf lettuce and mustard greens are also rich sources. Head lettuce and cabbage are relatively low, but cabbage greens and the outer leaves of cabbage rank even higher than turnip greens.

Experiments by Fincke[20] have shown that the calcium content of broccoli and that of cauliflower are nearly as available as that of milk. Speirs[21] has reported that the utilization of calcium from turnip greens is about equal to that from milk but that the calcium in tender greens, collards and kale is less well utilized. The calcium of spinach, beet greens, chard and lamb's quarters is not nutritionally available because of the high oxalic content of these vegetables.

The calcium contribution of green leafy vegetables becomes particularly important in diets containing little milk or cheese.

The green leafy vegetables are important sources of iron. A serving (3 ounces) of cooked turnip greens, mustard greens, spinach, chard or beet greens will supply approximately 25 per cent of the adult daily allowance. Kale supplies somewhat less and headed lettuce and cabbage are relatively poor sources.

The green leafy vegetables are all rich sources of carotene and thus make an important contribution to the vitamin A content of the diet. A range of 2,800 to 13,650 international units per hundred grams for kale, chard, spinach, turnip greens, dandelion greens and mustard greens has been reported.[7] The greener and leafier the product, the higher is the vitamin A content. Carotene from green leafy vegetables seems to be better utilized than that from the yellow vegetables. Allowing for losses in cooking and for the fact that the vitamin allowance must be higher when carotene is the source, a 3 ounce serving of one of these greens can be relied on approximately to meet the day's needs. Headed cabbage and lettuce are relatively poor sources.

20 Fincke, M. L. The Utilization of the Calcium of Cauliflower and Broccoli. J. Nutrition 22: 477 (Nov.) 1941.
21 Speirs, M. The Utilization of Calcium in Various Greens. J. Nutrition 17: [illegible] (June) 193[illegible]

In the fresh state the leafy vegetables are excellent sources of vitamin C A cup of raw shredded cabbage will furnish nearly a third of the day's allowance Watercress collards, broccoli turnip greens mustard greens and kale are similar in vitamin C content to cabbage, beet greens and dandelion greens contain somewhat less, lettuce escarole and endive contain much less Leafy vegetables lose vitamin C by oxidation in storage and also in cooking Further losses occur by solution in cooking if the cooking water is discarded Gould, Tressler and King[2] found that in cooking 25 per cent of the vitamin C of cabbage was destroyed by oxidation and another 25 per cent lost in the cooking water Other vegetables have shown similar losses In the preparation of vegetables further destruction of vitamin C by oxidation occurs when they are crushed or bruised or allowed to stand for long periods of time at room temperature both before and after cooking Cutting and chopping into small pieces also accelerates the oxidation of vitamin C but in order to reduce the cooking time it is sometimes advisable to do this with large vegetables particularly if they are cooked in very small amounts of water Vitamin C losses can be decreased by refrigerating the vegetables until ready to prepare and serve In cooking use as little water as possible have the water boiling to start with bring the water back to the boil quickly after adding the vegetables and keep the cooking time at a minimum The same methods which help to conserve the vitamin C value will also conserve riboflavin thiamine and mineral values All these food components are more or less soluble in water

Most of the green leafy vegetables are excellent sources of riboflavin the leaves being much richer than the stems A serving of cooked beet greens will supply about one fourth of the daily adult allowance Spinach and kale supply about one fifth Other greens supply a lesser amount headed cabbage and lettuce ranking at the bottom of the list Leafy vegetables are not a good source of thiamine furnishing only 3 to 15 per cent of the adult daily allowance The destruction in cooking usually does not exceed 10 to 15 per cent and when large amounts of water are used and discarded large additional losses occur by solution Certain leafy vege

22 Gould S, Tressler D K and King C G Vitamin C Content of Vegetables V Cabbage Food Research 1:427 (Sept Oct.) 1936

tables have been found effective in preventing and curing pellagra The following values have been reported for some of the green vegetables (mg per hundred grams) spinach 0.70 broccoli 0 90 cress 1 0 to 2 0 and kale 2 0

In the amounts commonly consumed leafy vegetables are of little significance as energy foods but their higher carbohydrate content provides roughage which is needed in certain diets They are relatively richer in protein than in calories and their protein ranks above seed proteins in general in biologic value However the actual contribution to the diet in the amounts commonly consumed is small

Miscellaneous Vegetables—There are several other vegetables which although limited as to general use make important contributions to the diet of certain groups The Hubbard or winter variety of yellow squash contains 5 000 international units of vitamin A per hundred grams One half cup of the cooked product supplies nearly one half the adult daily allowance Summer squash contains much less Pumpkin furnishes approximately one fourth as much as winter squash.

A serving of fresh asparagus (nonbleached) can furnish approximately one seventh the day s allowance of vitamin A and one sixth that of vitamin C It is also a significant source of calcium and iron Brussel sprouts are rich sources of vitamin C and also furnish significant amounts of iron calcium and vitamin A Cauliflower is notable for its content of ascorbic acid thiamine and riboflavin

One medium sized sweet pepper will furnish 630 international units of vitamin A and 180 to 200 mg of vitamin C Chili peppers whether fresh or dried are a good source of vitamin A. Fresh chili is an excellent source of vitamin C Some of the vitamin C is retained on canning Okra contains 740 international units of vitamin A per hundred grams Parsley which is used mainly for decoration is an excellent source of both vitamin A and iron. When fresh it furnishes some vitamin C

FRUITS

According to United States Department of Agriculture statistics the approximate per capita consumption of fruits calculated on the fresh basis is about 150 pounds (68 Kg) Of this total 75 per cent is consumed fresh and 15 per cent canned and the remainder is

divided between dried fruits and juices Apples out ranked all other fruits, representing over one fourth the total consumption But citrus fruits as a class exceed apples by 50 per cent or more The nutritive values of various fruits have been excellently summarized in an article by Morgan [23] and we have drawn on this article for many of the data which follow

Fruits do not contribute important amounts of either calories or proteins to the diet but they are of out standing value because of their content of certain vita mins and minerals As a class, fruits are important sources of ascorbic acid certain members of the B complex, vitamin A iron and other minerals but there is a large variation among the different kinds as regards the extent of their contributions

The citrus fruits are especially important for their ascorbic acid content A medium sized orange weighing about 5½ ounces (155 Gm) will meet the daily adult allowance A somewhat greater weight of grapefruit is required Four and one half ounces (130 Gm) of canned orange or lemon juice or 6 ounces (170 Gm) of canned grapefruit juice would supply the daily allow ance While the citrus fruits cannot be considered important sources of other nutrients, they do contain iron calcium and thiamine in amounts which are of some significance in the diet Pineapples, which are consumed mostly canned or as juice, contain about half as much vitamin C as do citrus fruits and are in general similar in other values

Apricots and yellow peaches are important sources of vitamin A The day's adult allowance is supplied by 3½ ounces (100 Gm) of fresh or canned apricots or by approximately three times as much fresh or canned peaches Weight for weight dried peaches and dried apricots supply approximately three times as much vitamin A as the fresh products Canteloupes contain about half as much of this vitamin as do fresh peaches and they are an important source of ascorbic acid being about equal to the citrus fruits Dried prunes furnish significant amounts of vitamin A riboflavin and thia mine Plums rank above other fresh fruits in thiamine content Apricots peaches and to a lesser extent prunes are significant sources of iron

23 Morgan A F A Nutritive Index of Fruits Fruit Products J 21 75 (Nov) 1941

Apples cannot be considered a large source of any vitamin or mineral nutrient In view of their large consumption however they do make a significant contribution of ascorbic acid to the diet A medium sized apple weighing 6 ounces supplies on the average about one tenth the day s allowance but there are decided differences among varieties The keeping qualities of apples makes it possible for them to be marketed throughout the winter in latitudes where fresh grown sources of vitamins are unavailable or high in price In rural areas in which they are produced home stored apples undoubtedly make an important contribution of ascorbic acid to the diet during the winter season, when the problem of getting adequate supplies of this vitamin is most difficult Apples also contain a significant amount of iron There is a 25 per cent loss of vitamin C in making applesauce The loss is greater when apples are baked or made into pie

Bananas are similar to apples in vitamin C value they contain almost twice the iron Bananas are a significant source of vitamin A

Fresh *strawberries are another food high in vitamin* C the range for eleven varieties being between 40 to 104 mg per hundred grams Thus one half cup would supply from two thirds to more than the daily need for ascorbic acid [24]

SUGARS SYRUPS AND MOLASSES

White sugar contributes only calories to the diet It is clear that the present large consumption of sugar is disadvantageous in that it means a smaller consumption of nutritionally superior foods Brown sugar corn syrup honey maple syrup and maple sugar contain small amounts of calcium and iron Honey contains small amounts of some of the B vitamins and vitamin C Molasses is an excellent source of both 1½ tablespoons furnishing approximately one tenth the estimated daily adult allowance of calcium and one fifth the estimated daily adult need of iron Sorghum supplies a lesser amount of calcium and about an equal amount of iron Table blend syrups contain a significant but lesser amount of iron

[24] Burkhart L and Lineberry R A. Determination of Vitamin C and Its Sampling Variation in Strawberries Food Research 7: 332 (July Aug) 194

VEGETABLE OILS

Cottonseed, corn, soybean, peanut and olive oils and in lesser amounts other vegetable oils are consumed as shortenings salad oils and margarines The oils as such are sources only of energy and essential fatty acids Many oleomargarines are now fortified with 15,000 international units of vitamin A per pound, they may also supply some vitamin D

CHAPTER XXVI

FOODS OF ANIMAL ORIGIN

PAUL E. HOWE

Animal foods play an important role in the diet of man. Nutritionally they are important sources of protein of good quality and excellent sources of vitamins and minerals. In addition animal foods are in general more distinctive in flavor and texture and often more palatable than foods of vegetable origin. However, grains and their products and vegetables continue to constitute the bulk of the diets of most persons because of their lower cost. The feeding of grains to animals and consumption of them as animal products is uneconomical in certain respects but many plant products can be consumed by human beings only after conversion through the animal. The customary combination of animal and vegetable foods is a sound practice nutritionally because of their supplementary relationship.

PROTEIN

Probably the most important contribution of animal foods to the human diet is the proteins (amino acids) they supply. The animal proteins generally are of high nutritive value although two proteins found in connective tissue of meat, collagen (gelatin) and elastin, are deficient in the essential amino acid tryptophan and are low in methionine, cystine, tyrosine and isoleucine. The quantities of these proteins in lean meat are so small however, that they have no pronounced effect on the over all nutritive value of lean meat. The proteins of whole egg are highly digestible and almost perfectly utilized as shown in experiments with both animals and man. Whole egg has therefore been used as a

standard with which to compare the amino acids from various foods or diets [1]

The relative nutritive values of proteins are deter mined not only by the kinds and amounts of amino acids they contain but also by their digestibility and avail ability to the body Determination of digestibility and availability requires studies with man or animals in addition to in vitro digestion experiments, the amino acid content is determined chemically and biologically

The approximate amino acid content of a number of animal foods and food products as assembled by Block and Mitchell [2] is given in table 1 [3] Data are provided for comparison on the amino acid content of wheat leafy vegetables and soya bean flour Given under the data of each protein are (*a*) the limiting amino acids in relation to the protein and the percen tage deficiency of whole egg (*b*) biologic values (*c*) the grams gain per gram of protein ingested (protein efficiency ratio) and (*d*) net utilization

The limiting amino acids have been corroborated in some cases by experiments with rats It has been shown that other acids may become limiting in turn after those in greatest deficiency are supplied The extent to which a protein is deficient in a diet depends on the amount consumed For example in beef only cystine or methionine is limiting at the 10 per cent level [4] At a 15 per cent level or on the addition of cystine or methionine the growth promoting value of beef becomes equal to that of egg protein The biologic values of the different kinds of muscle liver and kidney are similar

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1 Sahyun M Proteins and Am no Acids in Nut tion New Yo k Reinhold Publ sh ng Company 1948 Wohl M G Dietotherapy Clinical Application of Modern Nutr tion Philadelph a, W B Saunders Company 1945 Lew s H I Prote ns in Nut t on chap 1 of Handbook of Nutr tion A Sympos um Prepared Under the Au p ces of the Council on Foods and Nutrition of the American Medical Assoc ation to be publ shed.

2 Mitchell H H and Block R J Some Relationships B tween Amino Ac d Cont nts of Proteins and The r Nutritive Values for the Rat, J Biol Chem. **163** 599 6 0 1946

3 Additional Data Lyman C. M and Ku'ken K A Th Am no Acid Composition of Me t and Some Other Foods, Bulletin 708 T xas Agricultural Experiment Stat on 1949

4 Hoagland, R. Ell s N R Hankins O G and Sn der G G Supplemental Value of Certain Amino Acids for Beef Protein J Nutri tion **35** 167 176 1948

Table 1—*Approximate Amino Acid Composition* of Certain Animal and Vegetable Proteins (Calculated to 16 per Cent Nitrogen) Together with Indexes of Nutritive Value†*

	Whole Egg	Whole Milk Cows	Beef	Liver	Casein	Collagen (Gelatin)	Leafy Vegetables	Whole Wheat	Soya Bean Flour
Arginine	6.4	4.3	7.7	6.6	4.2	8.7	7.0	4.2	7.1
Histidine	2.1	2.6	2.9	3.1	3.0	0.9	2.1	2.1	2.3
Lysine	7.2	7.5	8.1	6.7	7.2	5.5	5.7	2.7	5.4
Tryptophan	1.5	1.6	1.5	1.4	1.2	0.0	1.9	1.2	1.2
Phenylalanine	6.3	5.7	4.9	6.1	5.0	2.1	4.5	5.7	5.7
Tyrosine	4.5	5.3	3.4	4.6	6.2	0.7	5.1	4.4	4.1
Methionine	4.1	3.4	3.3	3.2	3.5	0.8	2.3	2.3	2.0
Cystine	2.4	1.0	1.3	1.4	0.3	0.1	2.0	1.5	1.2
Threonine	4.9	4.5	4.6	4.5	4.1	2.0	4.1	3.3	4.0
Leucine	9.2	11.3	7.7	8.4	9.9	3.1	6.5‡	6.5	6.6
Isoleucine	8.0	8.5	6.3	5.6	6.5	1.7	2.5‡	2.9	4.7
Valine	7.3	8.4	5.8	6.2	6.7	2.5	4.1‡	4.5	4.2
Glycine	2.2	2.3	5.0		2.1	24.0			
Limiting amino acids		Cystine + methionine 32%	Cystine + methionine [illegible]%	Isoleucine 50%	Cystine + methionine [illegible]%	Tryptophan 100%	Isoleucine [illegible]%	Lysine [illegible]%	Methionine [illegible]%
Biologic value	94	90	[illegible]	77	[illegible]	25		67	[illegible]
Protein efficiency ratio	3.8	2.9	3.2	2.7	2.3		–	1.5	2.2
Net utilization.	94	86	76	75	68	24		61	[illegible]

* The approximate amino acid composition of a food may be obtained by application of the values in relation to the total nitrogen content. Thus if a sample of fat beef contains 12.5 per cent nitrogen, the amino acid value would be multiplied by 0.75 (12.2/16.0) to obtain the percentage composition of the amino acids.

† *Data from Block and Mitchell.*[15]

‡ Alfalfa.

The general nutritive values or quality of proteins or mixtures of foods are usually expressed either as the ratio of gain in body weight to the protein consumed or as biologic values in terms of the percentage of the protein nitrogen utilized by the body The product of the biologic value and the true digestibility gives a value for total utilization, or "net" utilization Mitchell and Block[5] have found a good correlation between the various methods of expressing the nutritive value of proteins They have suggested a method for scoring them based on the amino acids present in a protein as compared with the amino acids of the proteins of whole egg, which agrees well with the biologic values

The value of one protein in supplementing the deficiencies of another is important in providing an adequate diet It is the ability of the proteins of animal

TABLE 2—*Biologic Values and True Digestibilities of Food Proteins Determined in Man*[6]

	Biologic Value	True Digestibility
Egg whole	97 (9? 100)	96
Soya bean	81 (2 92)	80
Beef steak	84 (2-93)	97
Peanut	83 (6 9?)	93
Kitchen yeast	87 (76-96)	87
Cottonseed	91 (8? 103)	78

foods to supply lysine to meet the greatest deficiency of many vegetable foods, as well as the additional quantities of other acids and associated nutrients they contain that has made them so nutritionally valuable in the diet

The value of the proteins in pork and milk and of lysine as supplements to grain products is illustrated in a study with rats[7] Equal parts of animal protein nitrogen from pork or milk and vegetable protein from whole wheat, white or rye flour gave as good growth as

5 (*a*) Mitchell H H and Block R. J* (*b*) Block R J and Mitchell H H *The Correlation of the Amino-Acid Composition of Proteins with Their Nutritive Value* Nutrition Abstr & Rev **16**:249 78 1946

6 Murlin, J R, Edwards L E and Hawley E E Biological Values and True Digestibilities on Some Food Proteins Determined on Human Subjects J Biol Chem **156**:785 786 1944

7 Hoagland R Ellis N R Hankins, O G and Snider, G G: Nutritive Properties of Pork Protein and Its Supplementary Value for *Bread Protein Technical Bulletin 906 United States Department of* Agriculture 1945

pork or milk alone Mixtures of one third animal protein and two thirds vegetable protein gave nearly as good growth The addition of 1 per cent of lysine to white flour had almost twice the effect on the growth of rats as that of the flour alone

The need for a supplement to a diet varies with the quantity of protein consumed A protein low in certain amino acids may be satisfactory when taken in quantities sufficient to supply the required amount of the limiting amino acids This is true of both vegetable and animal proteins Most animal proteins at the 10 per cent level are deficient in the sulfur-containing amino acids cystine and methionine and support less growth than whole egg protein at the same level[4]

Beef protein is equal to egg protein however at the 15 per cent level or at the 10 per cent level if 0 2 per cent cystine or methionine is added The addition of phenylalanine leucine iso leucine valine or tryptophan which are also low in comparison with egg white with methionine or all of them together did not improve beef protein There is experimental evidence for the classic combination of ham with eggs[8] Ham fresh or cured at the 10 per cent protein level contains insufficient cystine or methionine for optimum growth of rats Combinations of equal parts of pork and whole egg or egg white protein or the addition of cystine or methionine to the pork gave growth approximating that of egg protein alone The addition of cystine to this mixture or to the ham alone gave better growth than egg protein alone

There is still much work to be done on the variations in the proteins themselves and on the effects of heat and chemicals on them These factors plus digestibility, utilization and the time of ingestion (simultaneously or alternately) may modify the results predicted from amino acid composition

Under certain conditions heat lowers the biologic value of animal and vegetable proteins The change does not always modify the amino acid content as determined by hydrolysis or by feeding of the hydrolyzed protein Lysine is particularly susceptible to

[8] Hoagland R Ellis N R Hankins O G and Snider G G Supplemental Relationship Between Pork Protein and Egg Protein J Nutrition 34 435 1947

combination or change by heat Casein,[9] liver,[10] and the cake mixture of Block and his co workers[11] are shown to have been modified by heat The nutritive value was restored by the addition of a suitable amount of lysine[11] The omission of one essential amino acid except arginine, from a complete mixture of amino acids resulted in a failure to maintain weight and loss of appetite in rats[12] Similar omission of essential amino acids in man resulted in negative nitrogen balances and loss of appetite[13]

The interrelationship of nutrients in metabolism which is demonstrated in present day research in nutrition seems to reemphasize the desirability for each meal s being complete The effects of a failure to supply the essential amino acids in the quantities and proportions required have been shown in studies with both animals and humans Cannon and co workers[14] and Wissler and co workers[15] have shown that rats attain nitrogen balance when an adequate mixture of amino acids is fed at one time but display a negative balance if an inadequate mixture is fed and the missing amino acids are supplied later even if fed at alternate hours Similarly it has been shown that when animal and vegetable proteins which supplement each other are fed together they support good growth, but when fed at different times in the day growth is retarded[16] Leverton and Gram[17] found in human subjects that

9 Greaves E O Morgan A F and Loveen M K The Effect of Amino Acid Supplements and of Variations in Temperature and Duration of Heating upon the Biological Value of Heated Casein J Nutrition **16** 115 128 1938

10 Seegers W A and Mattill H A The Effect of Heat and Hot Alcohol on Liver Proteins J Biol Chem **110** 531 539 1935

11 Block R J Cannon P R, Wissler R W Steffee C H Straube R L Frazier L E and Woolridge R L The Effects of Baking and Toasting on the Nutritive Value of Proteins Arch Biochem **10**: 295 301 1946

12 Frazier L E Wissler R F Steffee C H Woolridge R L and Cannon P R Studies in Amino Acid Utilization The Dietary Utilization of Mixtures of Purified Amino Acids in Protein Depleted Adult Albino Rats J Nutrition **33** 65 84 1947

13 Rose W C The Role of Amino Acids in Human Nutrition Proc Am Philo Soc **9** 11 116 1947 Rose W C Amino Acid Requirements of Man Federation Proc **8** 546 552 1949

14 Cannon P P Steffee C H Frazier L J Rowley D A and Stepto R C The Influence of Time of Ingestion of Essential Amino Acids upon the Utilization in Tissue Synthesis Federation Proc **6**: 390 1944

15 Wissler R W Frazier L E and Slayton R E Influence of Time of Ingestion of Essential Amino Acids upon Maintenance of Nitrogen Balance Proc Soc Exper Biol & Med **7**~ 589 591 1949

16 Geiger E The Role of the Time Factor in Feeding Supplementary Protein J Nutrition **36**: 813 819 1948 Editorial Nutrition Rev **5** 316 1947

17 Leverton R M and Gram M R Nitrogen Excretion of Women Related to the Distribution of Animal Protein in Daily Meals J Nutrition **39** 57 1949

nitrogen utilization was affected by the distribution of protein in the diet. Subjects who received an adequate mixture of amino acids divided equally between three meals had a positive nitrogen balance, whereas those who ingested the same amount of amino acid mixture divided into two meals had a negative balance. For a full understanding of factors affecting protein metabolism in the human being more study will be required.

CALORIES AND FAT

The energy value of animal foods is primarily related to the fat content. Most fresh animal foods have a high water content and when freed of external fat are relatively low in energy. It is therefore possible to change the fat content of most animal foods and thus their caloric value by mechanical separation of the fat rich portion and thus to obtain protein products low or relatively low in fat, e g, lean meat, skim milk and egg white. In fish the fat is deposited largely in the flesh. Some fish such as haddock and cod are always low in fat while the fat content of others varies with the season. Mackerel for example are low in fat in the spring, 1 to 2 per cent fat, and high in summer, 6 to 17 per cent fat. Poultry flesh is also low in fat, the breast lower than the leg.

As an animal fattens the subcutaneous fat increases more rapidly than that in the muscle. Tables showing the composition of meats usually refer to edible meat which is the combined muscle tissue and subcutaneous fat. Whether the fat is actually eaten depends on habit. There are times in choosing foods, evaluating diets or planning low fat diets when it is desirable to know the fat content of the lean meat itself as well as that of the whole cut. Table 3 gives the approximate fat content of the total edible portion as presented in the table of food composition of the United States Department of Agriculture[18]. The values given here have been calculated with equations developed by

18 (a) Chatfield, C, and Adams, G. Proximate Composition of American Food Materials. United States Department of Agriculture Circular 549, 1940. (b) Bureau of Human Nutrition and Home Economics with National Research Council. Tables of Food Composition in Terms of Eleven Nutrients. Miscellaneous Publication 572, 1945. (c) Sherman, H. C. Foods of Animal Origin. Handbook of Nutrition. A Symposium. Chicago: American Medical Association, 1943, chap. 13, p. 259.

Callow[19] The values given refer to the total muscular tissue and are typical of the average lean meat portion of the carcass In general for animals of the same degree of fatness, the muscle, or lean, tissue in beef is fatter than it is in mutton and in mutton fatter than in

TABLE 3—*Approximate Fat and Protein Content per 100 Gm of Animal Products Modified by Removal of Separable Fat or Low in Fat* *

		Total Edible Portion		Muscle Tissue (Lean) or Nonfat Portion		
Food	Subclass	Fat (Ether Ext) Per centage	Separable Fat † Per centage	Fat † (Ether Ext) Per centage	Protein † Per centage	Calories
Beef	Thin	14 0	18	3 2	20 1	109
	Medium	22 0	25	4 6	19 8	1.1
	Fat	28 0	31	5 7	19 6	130
	Very fat	39 0	41	7 7	19 1	146
Lamb	Thin	14.8	19	3.3	20 0	110
	Intermediate	27 7	6	5 7	19 6	130
	Fat	39 8	42	7.9	19 1	148
Pork	Thin	35 0	38	7 0	19 3	140
	Medium	45 0	47	8.8	18 9	155
	Fat	55 0	56	10 6	18.5	169
Veal	Thin	8 0	13	2 1	20 3	100
	Medium	1 0	16	2 8	20 1	106
	Fat	16 0	20	3 5	20 0	112
Poultry		10 9				
	Breast			1 1	0 5	104
	Leg			4 4	20 1	120
Rabbit	Dressed	8.		1 1	20 8	175
Fish	Cod (haddock)			0 4	16 5	70
Milk		3 8	3 9			
	Skim			0 1	3 5	15
	Buttermilk			0 4	3.5	13
	Dry skim	6 0 (whole dried)		1 0	6 8	156
Cheese	Cottage			0 8	19.2	84

The unmodified foods are those referred to in Tables of Food Composition United States Department of Agriculture[18b]

† Estimated for the muscle tissue of the edible portion of the entire dressed carcass by equations developed by Callow[1]

swine This difference is due primarily to the fact that the amount of intermuscular fat ranks in the following order beef sheep and swine

There is considerable variability in the fat content of the various commercial cuts of meat The data in

19 Callow E Comparative Studies of Meat I The Chemical Composition of Fatty and Muscular Tissue in Relation to Growth and Fattening J Agricultural Sc 37 113 129 1944

table 4 illustrate the variation in the fat content of cuts of lamb Beef and lamb show similar variations in fatness of lean in relation to total fatness [20]

The fat content of the muscle tissue of round of beef approximates that given in table 3 for the total muscle tissue of the carcass for the same degree of fatness The fat content of the rib eye muscle of these rounds however, was 6 to 10 per cent higher While the fat content of the rib-eye tends to be greater with increasing fatness of the carcass this does not always hold The fat content has been found to be from 5 to 10 per cent in animals of approximately the same over all fatness Analyses of the lean of fresh ham show that it is approximately 2 to 3 per cent lower than the fat content of pork muscle given in the table Data are included in the table on the fat content of milk fish and rabbit to indicate the possibility of obtaining a high protein, low fat diet from foods from these sources

TABLE 4—*Percentage of Ether Extract (Fat) in the Lean of Commercial Cuts of Lamb*

Grad	Total Carcass	Leg	Rib	Shoulder	Loin	Breast	Neck
1	36	7	20	16	11	14	16
2	26	6	16	11	11	11	11
3	22	6	14	12	9	9	8

Most natural animal fats contain the essential fatty acids, linoleic linolenic and arachidonic acids [21] The quantity present in the body and milk fat varies with the nature and amount of the feed given animals They are present in most of the liquid plant oils The body fats characteristic of animals when synthesized from carbohydrates and proteins and not derived from ingested fats are composed chiefly from palmitic oleic and stearic acids

In general the fats of animal products are 97 to 99 per cent digestible Variations in digestibility are related to the proportion of the long chain fatty acids with higher melting points such as stearic arachidic and palmitic acids which are present in the natural fats or produced by hydrogenation of unsaturated fatty

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[20] Bureau of Animal Industry United States Department of Agriculture unpublished data

[21] Burr G O and Barnes R H Non Caloric Functions of Dietary Fats Physiol. Rev 23: 256-273 1943

acids During the first four hours after ingestion fats like butter and liver oil are found to be absorbed more rapidly than lard, corn oil or partially hydrogenated fat In rats there was no difference in amount absorbed at the end of twelve hours The effect of the presence of fat in the food whether present in the natural food or added in preparation, on the rate of passage of food from the stomach is as important a factor in the utilization of fat in the diet as the digestibility [3] Dietary calcium and magnesium also reduce the digestibility of fats [24]

VITAMINS

Animal foods are generally good sources of the water soluble vitamins of the vitamin B complex Milk contains less thiamine and niacin than meat and more riboflavin than meats with the exception of lamb When milk is used in the quantities required to supply the major source of calcium it contributes a large proportion of the riboflavin necessary Eggs are rich in riboflavin and thiamine and low in niacin and while eggs are used in relatively small quantities they make a fair contribution to the total vitamin requirements Liver and kidney are generally rich in all the vitamins of the B complex Liver also contains nutrients known to be required by experimental animals but less well established for man Fish is lower *in the vitamin B complex than most meats* or milk Chicken is relatively rich in niacin

Animal products contain vitamin A or carotene the precursor of vitamin A The fats of milk eggs and liver are unusually rich in vitamin A The *natural* yellow color of milk generally higher in summer represents carotene The yellow of artificially colored butter however is not due to the presence of carotene

22 Langworthy C F The Digestibility of Fats J Indust Engin & Chem **15** 276 278 1923 Hoagland R and Snider G G Digestibility of Certain Higher Saturated Fatty Acids and Triglycerides J Nutrition **26** 219 2 5 1943 Holt L E Jr Tidwell H C Kirk C M Cross C M and Neal S Studies in Fat Metabolism Fat Absorption in Normal Infants *J Pediat* **6** *427 1935* *Cowgill G R. Relative* Nutritiv Value of Animal and Vegetable Fats Physiol Rev **23** 664-686 1945

23 Steenbock H Irwin M H Weber J The Comparative Rate of Absorption of Different Fats J Nutrition **12** 103 111 1936

24 Cheng A L S Morehouse M G and Deuel H J Jr The *Effect of the Level of Dietary Calcium and Magnesium on the Digestibility* of Fatty Acids Simple Triglyceride and Some Simple Natural Hydrogenated Fats J Nutrition **37** 237 50 1949

nor is the natural yellow of egg yolk The yellow fats of cattle which occur when the animals are fed on grass, are due to carotene and hence such fats are better sources of vitamin A than white fats Fat of cattle fed on grass contains 660 international units of vitamin A as compared with 33 of vitamin A in the fat of cattle on a low carotene ration The fats in muscle or lean meat contains chiefly vitamin A rather than carotene [25]

The quantity of vitamins in animal foods varies with the nature of the ration fed and in part with the breed or kind of animal as was shown with regard to carotene Pork tends to be richer in thiamine than other meats The relative uniformity of the vitamin content of the products of the herbivorous animals results in part from the production of vitamins in the intestinal tract The animal protein factor which appears to be vitamin B_{12} is in part at least, produced by micro organisms in the intestinal tract

The vitamin D content of both milk and eggs is determined by the kind of feed used or by exposure to sunlight The concentration of vitamin D in both these foods and in butter is assured by incorporation of this vitamin in the feed or in the case of milk by irradiation or by addition of vitamin D to the milk Margarines are usually fortified with vitamin A carotene or both in quantities to assure 15 000 international units per pound When vitamin A is added the amount is stated on the label

Many animal foods are good to excellent sources of water soluble vitamins and other factors which have been identified but for which human requirements have not been established

INORGANIC ELEMENTS

Both animal and vegetable foods are good sources of phosphorus and provision for adequate intake of the mineral is not a problem in the average diet Phosphorus is associated with proteins, so that the phosphorus intake is roughly proportional to the protein intake

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25 Cabell C A Ellis N R and Madsen N L Vitamin A Activity of Lean Meat and Fat from Cattle Fed Various Levels of Carotene Food Res 8 496 501 1943

Of the animal foods, milk and most milk products are particularly rich in calcium Cheese and dried skim milk are rich in calcium and make an important addi tion to the calcium requirement when eaten as such or combined with other foods Eggs, while fairly rich in calcium, are seldom eaten in sufficient amounts to supply a major part of the calcium requirement

Neither meat nor fillet of fish are important sources of calcium It is only when the bones of fish are con sumed as in canned sardines and salmon and when such foods supply a major part of the protein that they make an important contribution to the calcium intake In some countries dried and canned fish meals and fermented fish containing bones are important sources of calcium Calcium is also obtained from the bones by some methods of cooking and finely ground bone meal has been incorporated in canned ground meat or meat mixtures in some countries A preparation of extremely finely divided bone is being used in the manufacture of some special foods and confections as a contribution both to texture and to greater calcium content

Animal foods supply variable quantities of iron where considerable quantities of meat and eggs are used, they may supply up to half of our daily require ment Both milk and fish are low in iron The iron content of animal foods is associated with the protein The milligrams per hundred grams of protein are meats 15 (varying from approximately 8 for pork and lamb 12 for beef and veal 25 for heart to 117 for kidney), eggs 24 fish 5 5 and milk 9 0

PROCESSING AND STORAGE

Animal foods are processed to prevent deterioration to facilitate transportation and storage and to provide a variety of attractive mixtures The commonest methods of preservation involve heat cold drying and other deterrents to oxidation or bacterial growth Canning bottling and packaging are also used to provide mechani cal protection of the food and to prevent oxidation loss of moisture or contamination after processing Each process modifies the character of the fresh material and may result in some loss of nutritive value

Refrigeration is used to preserve food for limited periods of time The introduction of quick freezing and low temperature storage makes it possible to keep

foods safely in a state approximating fresh food for longer periods of time if protected against oxidation Frozen foods are particularly vulnerable to bacterial contamination when thawed and allowed to stand at room temperatures Frozen foods retain their nutritive value. There is a slight improvement in the tenderness of frozen meats, provided they have been held long enough before freezing for rigor mortis to disappear [26]

The use of heat in canning and drying tends to reduce the nutritive value of animal foods but with a few exceptions the changes that occur with modern methods of processing are approximately of the same magnitude as those that occur in home preparation The extent of the changes depends on the time and temperature of heating The average losses in nutritive value of the diet during the processes of food preparation and service have been estimated to be thiamine 40 per cent riboflavin 15 per cent niacin 20 per cent and ascorbic acid 35 per cent In the case of vitamins the losses in quality of canned or dried foods occurring during long storage and the subsequent reheating at the time of use may be greater than those in the original processing There may also be loss of quality during storage at high temperatures for a long time

The nutritive value of the proteins of animal foods is not seriously affected by the ordinary methods of food preparation or sterilization in canning according to results obtained with rats Some decrease in the biologic value has been demonstrated as indicated in the discussion of proteins The effects of baking and toasting on the nutritive value of a protein mixture made into a cake have been reported [11] Here the mix consisted of flour, sugar egg white, lactalbumin, hydrogenated vegetable oil dried yeast molasses and salt with 25 per cent of the calories from protein The mix had a high protein efficiency 3 3 to 3 5 but the value decreased to 2 5 when the cake was baked When the cake was dried in the oven over night the protein efficiency fell to less than 1 5 and when slices of the cakes were toasted 40 to 60 minutes until they had the appearance of commercial rusk the value became less than 0 7 The changes involved chiefly the availability

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[26] Hankins O G and Hiner R L. Freezing Makes Beef Tenderer Food Industries 12 49 51 1940

of lysine, for when 0 63 per cent lysine was added to the toasted cake the initial nutritive value was practically restored A study of the possible effect of nitrite used in curing meats on the destruction or inactivation of lysine was made in relation to pork luncheon meat[27] There was no loss of lysine in cooking (canning) of fresh meat, but there was a loss of 12 per cent of lysine in the cooked cured meat When the fresh canned-uncured and canned cured meats were fed at a level at which lysine was the limiting nutrient, there were no significant differences in the growth of rats thus indicating that such inactivation or destruction of lysine as occurred was not sufficient to be detected in feeding experiments

Experiments with lactalbumin and mixtures of amino acids indicate that the lowered nutritive value due to heating, either dry in the oven or moist in the autoclave, may affect the availability of the protein rather than inactivation of lysine[28] Pure lysine was however not affected by the temperatures used when heated alone or in a mixture of the essential amino acids In this case the change was produced at a lower temperature and in less time when the protein was heated in the autoclave than when heated in a dry oven There is a slight reduction in lysine from 8 9 to 7 8 Gm per hundred grams in the heat processing of evaporated milk[29]

There is considerable evidence that the ordinary processes of cooking and processing of foods for human consumption do not seriously affect the nutritive value of the proteins in the amounts used in the average mixed diet The results of changes in the amounts used in the nutritive value of canned meats[30] and milk[31] are not pronounced with respect to their biologic values There is, however, no experimental evidence as to the

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27 Wilder O H M and Kraybill H R Effect of Cooking and Curing on Lysine Content of Pork Luncheon Meat J Nutrition **33**: 235 242 1947

28 Davis R. M Rizzo P and Smith A H The Effect of Heat on the Nutritive Value of Lactalbumin I Growth on Diets Containing Heated Proteins J Nutrition **37** 115 126 1949

29 Hodson A Z and Kreuger G M Essential Amino Acid Content of Casein and Fresh and Processed Cow's Milk as Determined Microbiologically on Hydrolysates Arch. Biochem **10** 55 63 1946

30 Rice, E E and Robinson H E Nutritive Value of Canned and Dehydrated Meat and Meat Products Am J Pub Health **34** 584-592 1944

31 Knott, E. Thiamine Content of Milk in Relation to Vitamin B1 Requirement of Infants Am. J Pub Health **32**: 1013 1942

effect of processing on the protein of canned and dried animal foods when used as supplements to vegetable foods over long periods of time, such as could occur under unusual conditions

The manufacture of digests or hydrolysates of proteins for special feeding or for intravenous injection is an important phase of animal food processing Studies of amino acid requirements of man and animals have shown that such mixtures are utilized and may have biologic values approximating those of the proteins from which they are made[32] The developments in amino acid requirements will enable manufacturers to correct partial shortages in amino acids and to improve the relations between them to obtain the greatest efficiency of utilization on intravenous injection

Considerable losses in the vitamin content of processed animal foods occur in home preparation and processing and in subsequent storage Thiamine and pantothenic acid are both soluble in water and destroyed by heat The losses are greater at high temperatures and increase with the length of time of heating or storage or when kept warm for a period before serving The vitamin losses in meats in dehydration and canning are approximately as follows thiamine 30 to 40 per cent, riboflavin 0 to 10 per cent, niacin 0 to 10 per cent and pantothenic acid 20 to 30 per cent[30] Canned pork and dehydrated beef and pork show little further loss in riboflavin, niacin or pantothenic acid during storage for seven months at 99 F Slow losses of riboflavin and pantothenic acid occur in storage at 120 F Thiamine shows some further loss in storage at 80 F and may be half gone in seven months while at higher temperatures and/or long storage it is almost completely lost

The thiamine content of milk is reduced in evaporating and storage[31] It is reduced 23 to 35 per cent during evaporation and canning and may lose another 50 per cent on storage for a year

When canned or processed foods are recooked, as is too often the practice and held at a warm temperature a long time before being eaten as is sometimes done in

32 Albanese A. A Holt L. E Jr Davis V I Snyderman S E. Lein M and Smetak E M The Biological Value of Meat Hydrolysate in the Infant, J Nutrition 36: 133 138 1948 Albanese A A, Holt L E Jr Iroy V Snyderman S E. and Lein M Studies on Protein Metabolism in the Infant The Comparative Biological Value of Some Milk Protein Preparations Bull Johns Hopkins Hosp 80: 149 1947

restaurant and hospital kitchens, there are further losses in thiamine in addition to those which have already occurred

The importance of the deterioration in nutritive value of animal foods during home preparation and in processing depends on the contribution to the diet expected of them and on the quantities in which they are consumed The basic concern is with the attainment of nutritive requirements under the conditions which exist and one must measure the whole diet by this yardstick rather than consider changes in some foods without relation to the other foods consumed Processed foods will continue to be valuable foods and, as with proteins, the changes which occur in them are not sufficient to produce an inadequate diet in the quantities ordinarily consumed Likewise, with regard to losses of thiamine, if suitable quantities of enriched bread or potatoes or low extraction grain products are used the diet may still be adequate One must keep in mind, however, that losses in nutritive value during processing and food preparation could be serious under some conditions

CHAPTER XXVII

FOODS FOR EMERGENCIES

RUSSELL M WILDER
and
THOMAS E KEYS

Writing in 1942 on the subject 'Unusual Foods of High Nutritive Value' we urged reevaluation of supplies of food with emphasis on a number of resources which theretofore had not been tapped extensively and which warranted more consideration in developing plans for feeding populations for which supplies of food were limited The undernutrition of hundreds of millions of the European population precipitated by the war and scarcely arrested if at all since the ending of hostilities, prompts reiteration of this subject Also a number of foods which we considered in our previous paper have assumed immense importance in many of the war torn countries and some account of this experience is now available for review

Two general observations relate to this experience, each of them has been repeatedly affirmed The first is that starvation in the European countries bad as it has been has everywhere been less than was anticipated from estimates of food supplies available The second is that deficiencies of specific nutrients and especially deficiencies of vitamins have been relatively inconspicuous The reasons include the fact that persons who are undernourished compensate to some extent by curtailing their activities Children are less active in their play and the work output of adults falls unconsciously The growth of children is retarded Likewise with subnutrition goes depression of basal energy exchange, in starvation the basal metabolic rate may be as low as minus 40 which represents a physiologic adjustment The need for calories is restricted by these means and loss of weight lags behind what would be expected were judgment limited to knowledge of the calories available Also in consequence of diminished expenditure of energy the

requirement for several nutrients is lessened and the appearance of signs of gross deficiency, either of vitamins or protein, is postponed However, there is yet another reason for discrepancies between the loss of body weight anticipated and that observed This namely has been the ability of starving populations to supplement their diets with edibles which are not included *in customary estimates of food supplies* Thus some extra calories are obtained and in addition, as a rule, the unusual foods consumed are often good or even excellent sources of minerals and vitamins Thereby the diet as a whole in many European countries although inadequate with respect to calories and providing much less animal protein and less fat than is desirable, has been relatively improved in certain instances with respect to minerals and vitamins Exceptions have been noted In Spain, where for many people the staple foods were white bread and polished rice, the number of cases of mental and nervous disorders attributed to deficiency of B vitamins is reported to have increased greatly, in contrast to experience in Leningrad and Stalingrad where hundreds of thousands died of starvation but vitamin deficiency was not apparent

We made comment in our previous paper that the diets of primitive populations with food selection limited to unsophisticated foods, compared most favorably with the diets of those nations which are most advanced in general culture and whose people have certain silly notions about what is fit for food Primitive man was constantly in danger of starvation from inadequate supplies of food but the foods which he obtained from his natural environment were relatively rich in vitamins in minerals and in protein A happy custom of primitive man was to eat the entire carcass of his kill including the intestine which with the organ meats notably the liver was rich in vitamins He ate these morsels first by preference he drank the animal's blood he was none too squeamish in his taste for fish but took whatever he could catch and ate it whole Snakes and rodents were delicacies and insects termites and the like all rich in nutrients of the highest value were quite acceptable Wild fruits and vegetables were consumed either fresh as found or after a minimal period of storage Later with the development of agriculture the cereal grains came into use but so long

as milling methods remained primitive these provided much more nutrient material than is obtainable from the highly processed cereals of modern mills

The inhabitants of the European countries overrun by Germany reverted so far as they were able to the food ways of primitive people Many products which in normal times were not considered fit for human use have been found acceptable in this time of need The wheat and other grains available were ground whole for human use or milled to high rates of extraction whereby for example from 100 parts of wheat from 85 to 100 parts of flour are produced as compared to the 65 to 72 parts of flour yielded as white flour by the modern flour mill No skim milk was allowed to go to waste and the whey obtained from making cheese was utilized for food Organ meats were cherished and in places even the blood of slaughterhouse animals was consumed The populations of Europe were handicapped in this reversion to more primitive food ways by ingrained habits by taboos by lack of ingenuity and by numbers The natural food environment of Europe may have provided enough in primitive times but it falls far short of being ample for a population like that of modern Europe Nevertheless something could be done to eke out meager rations and what was obtained by these and other means helped to alleviate the worst effects of famine

The bread is dark and soggy made of several kinds of coarse grain reads one report Other than the rationed foods and they provided only 1 500 calories daily people could buy sea gulls crows and strange fish which formerly were considered unfit for human consumption Meat had disappeared even horse meat The women and children scoured the fields and road sides for edible plants The forests were finecombed for mushrooms and berries Dandelions nettles acorns leaves and nuts all had their uses Every little plot of ground even every window box became a victory garden That was in Norway In Holland tulip bulbs and sugar beets were consumed as food Both caused diarrhea when taken in large amount Rhubarb leaves proved toxic The same was true of beechnuts Thus at times more harm than good resulted from the practice of foraging In Germany in the spring of 1947, when coarse bread was made from high extrac-

tion flour, this bread and potatoes were the foods principally responsible for a nutritional situation which otherwise would have been more serious than should have been expected from the ration The diet largely consisted of bread and potatoes with a few beans and peas, a bit of cheese and a few onions The fat allowance was 9 Gm a day for adults The weekly meat allowance was usually consumed at one meal

EDIBLE WILD PLANTS

Weeds and other plants have been used as food by every famished population The varieties available in Belgium were described by Hermans The Russians resorted to cooking inedible greens to make a paste rich in carotene This was eaten as a spread on bread Sources of vitamin C were short in many countries In England as well as on the Continent rose hips were collected and reduced to syrup or jelly Pomegranate boiled and concentrated was used in Russia Germinating grains have long been known to be a source of ascorbic acid United States soldiers in the Pacific area were given a manual issued by the War Department which illustrated and described both edible and poisonous plants It was intended as a guide for soldiers separated from their units and dependent on foraging for their survival The manual covered all Polynesia Micronesia Melanesia the Malay Peninsula and the Philippines For practical purposes it also covered Indo China Thailand Burma and Eastern Asia An astonishing number of herbs ferns palms grasses tuber seeds and fruits were described as being edible and nutritious

Issued in 1943 by the Office of War Information of the United States government was a list of edible weeds with directions for their preparation Mentioned were dandelion lamb s quarters plantain poke purslane wild chickory and dock Some of these are to be found in every vacant lot and on other neglected ground Others grow abundantly along roadsides and hedges or by streams and in the woods A leaflet containing similar information was distributed by the New York Department of Health Mentioned in it were milkweed stinging nettle summer mustard and sorrel Mentioned also in a reference was a book entitled 'Weeds' by W C Muenscher

Among the edibles in nature which in emergencies can serve as food is the acorn which held a place of importance in the diet of the American aborigine After parching over coals the meat is sweet and palatable It may be powdered to make a flour Many wild plants served the Indians and early settlers of America Among those noted by Carr are the tuberous roots of the catbrier or greenbrier (Smilax) the roots of the common cattail the bulb of the sego lily and persimmons and poke week

KITCHEN GARDENS

The kitchen garden has made an important contribution through these recent years of shortages of food in Europe and gardens in America have helped to supplement the diet here and thus to release less perishable foods for export Greater savings of food for export can be made by avoidance of waste, not only waste of food itself but loss of the nutrients in foods during their handling and preparation in the kitchen Efforts to teach this lesson during the war were not without effect The problem is of supreme importance but not a part of the subject of this paper By its national gardening program the Department of Agriculture is encouraging the continuation of the wartime garden program City planners are encouraged to provide small garden plots for use by urban dwellers Not only is the contribution of fresh food from the garden of the greatest value in nutrition because fresh foods contain vitamins some part of which is lost when the foods are shipped to distant markets, but from the gourmet's point of view fresh foods contribute greatly to the attractiveness of the meal No tomato tastes as good as one just picked no lettuce no sweet corn no peas or green beans no strawberries or melons can compare with those grown in one's own garden Also the variety of food that can be made available is much greater than can be found in local markets Millions of city and suburban dwellers with no previous experience became skillful gardeners in the war years and learned that gardens pay in increased health and satisfaction Also many persons for the first time in their lives learned to eat these wholesome foods

In England in the war the Ministry of Food allotted land from parks and other open spaces and provided blueprints for the gardens The allotments were 10 perches" in size, a plot of about 300 square yards say 30 by 90 feet (9 1 by 27 4 meters) A study of ninety eight of these allotments showed an average production in one year of 411 pounds (186 4 Kg) of potatoes and 1 088 pounds (493 5 Kg) of other vegetables The plan involved successive plantings so that in the English climate it was possible to obtain a fairly even supply of products over the year The amount was sufficient to meet the requirements for vitamins C and A for a family of five and to add importantly to the supply of other nutrients and calories

POTATOES

Of all the vegetables however, the one which aided most in the support of human life in war torn Europe was the white or Irish potato The Ministry of Foods in England guaranteed the growers a price for all sur plus potatoes Their distribution was well controlled and they contributed to the calories of the diet even more importantly than wheat Drummond called bread and potatoes buffer energy foods' because at the height of rationing in the United Kingdom they remained in adequate supply, unrationed, to serve as buffers for diets which otherwise would have been too low in calories

The potato thus is properly regarded as a food of great value in emergencies Unfortunately, the crop is not entirely dependable and when great reliance has been placed on it failure of the crop has resulted in widespread famine Another problem with potatoes is the high water content and thus the cost of trans portation This has limited the usefulness of potatoes for relief feeding abroad The ocean freight alone is enough greater than that of flour so that flour at a cost of 6 cents a pound (13 2 cents a kilogram) has been less expensive than potatoes delivered free of charge to United States ports Potatoes furthermore are sensitive to freezing Great losses occurred in storage in Europe in the cold weather of 1942 1943

For the several reasons mentioned it would seem to be desirable to provide for large scale processing of potato crops Dehydration is a possibility but is rela tively expensive Potato flour can be made rather

inexpensively and has been reported as selling in a competitive market at only 8 cents a pound (17 6 cents a kilogram) which puts it in a class with wheat flour Uses for potato flour should be thoroughly explored Its admixture with wheat flour in making bread is a long established practice although little used since World War I Many other uses could be found Potatoes when properly prepared for eating make important contributions to the ascorbic acid content of the diet Potato flour probably contains no ascorbic acid but this difficulty could readily be corrected by suitable fortification The niacin and thiamine of potatoes are presumably retained in processing to flour Only about 40 per cent of the nitrogenous substance of potato is protein The balance consists of amides amino acids and purines yet the biologic value in nutrition although less than that of casein is said to be superior to that of the combined nitrogenous substance of wheat of which 90 per cent consists of protein The principal protein in potato (tuberin) is not superior in value to the proteins of wheat from which Chick and Cutting have concluded that some portion of the nonprotein nitrogenous material must be utilized as protein

PROTEIN RESOURCES

Shortage of protein of good biologic quality has been serious in many parts of Europe as well as in the Far East

Blood —In the winter of 1944 1945 plasma obtained from slaughterhouse blood played a part in Amsterdam in the treatment of famine edema A pediatrician was the first to call for it He wanted it for children in the 6 to 14 year age group in which the mortality rate had risen rapidly from the time that supplies of rationed milk had been suspended Two butchers were placed under supervision for the preparation of this plasma Soon thereafter general practitioners began to use the product for patients with hunger edema Benefit was observed with as little as 500 ml per week The fact that a dose of 6 Gm of animal protein a day which was all that this provided was lifesaving led to the conclusion that lack of certain essential amino acids in the almost entirely vegetable diet had been responsible for the edema and for increased mortalities The demand for the plasma increased so much that all slaughterhouse

blood was used for this purpose It was fed at first cooked in pancakes, later as bouillon or in brown bean soup Whole blood, incorporated in sausage (Blut wurst), which had been consumed before in parts of Europe, was not acceptable in Amsterdam Physicians however, prescribed it for anemia In Russia and in parts of Germany whole blood was used in bread In Switzerland, a mixture of potato and blood was recom mended

Fish—The normal catch of fish by European fisher men was seriously diminished while war lasted, owing mainly to confiscation of trawlers and other fishing boats for wartime purposes Fishing now is being stimulated by every means available in order to increase the supplies of protein Unfortunately only a rela tively small proportion of the normal catch of fish is at present utilized for food The balance is diverted to fishmeal fertilizer or is thrown away The protein of this waste was separated by Deuel for study of its biologic activity It equaled casein in potency for regenerating plasma protein in animals made hypopro teinemic by exsanguination

In addition to their value as a source of protein, small fish offer the advantage of containing edible bones, thus serving as a source of calcium A report from India by Basu and his associates contained the account of a study of calcium balance made on human subjects who were given small whole fish as the only source of calcium A daily intake of 70 Gm maintained a positive balance Calcium deficiency is prevalent in the rice eaters of Bengal and other parts of India where milk is not obtainable and an active interest in this matter is apparent from numerous studies reported in the scientific literature of India Aykroyd in a con sideration of Indian diets pointed to the fact that India of necessity must be self contained as regards food supply and that the existing relation between popula tion and the land necessitates a national diet composed of foods giving a high calorie return for each unit of the land Attempts to increase the production of foods not falling within this category foods such as milk or meat present great difficulties Adolph writing on conditions in China before the war made the comment that vegetarian people are usually vegetarian not because of dietetic whims but for economic reasons The

equilibrium between food supply and population is so delicate that disturbance of the status quo may be at once reflected either in emigration or in a mounting death rate from starvation Cereals and legumes provide some 88 per cent of the calories consumed in China This type of situation seems to us to call for great expansion of the fisheries, with due attention paid to Deuel s suggestion for more economy in the utilization of the catch It can be maintained that an increase of the food supply in the Orient would only lead to further increase of the population Our suggestion here however, is not so much an increase of the total calories but rather an improvement in the quality of the diet

The amount of animal protein obtainable from the sea is almost limitless Areas in which life is of unusual abundance are the North Sea the Norwegian Sea the waters around Newfoundland and off many of the coasts of all the continents The yield of coastal waters can be increased by fertilizing This was shown for instance by an experiment in Scotland An inland lock or bay of salt water with an area of about eighteen acres and an average depth of 2 meters was fertilized with so little as 600 pounds (272 2 Kg) of sodium nitrate and 400 pounds (181 4 Kg) of superphosphate A neighboring lock received no fertilizer There was an immediate rise in the vegetation of the fertilized lock to three to four times the original amount and the growth of fish leaped upward Baby flounders grew in thirteen months to a size equal to that of two or three years growth in the North Sea itself a rich feeding ground

We mentioned in our earlier paper the carp culture of German inland lakes The fish farms of Central Europe produce as much as 500 pounds (226 8 Kg) of fish per acre which has been compared to the 200 pounds (90 7 Kg) of beef or mutton obtainable from pasture land of quality A bulletin of the Department of Agriculture explains how to manage farm fishponds for food production

Soy Beans Peanuts Wheat Germ and Corn Germ — Protein of relatively high biologic value is provided by beans and peas Early in the emergency created by the war, production goals for soy beans were raised for two important purposes (1) for the oil to replace the

diminishing supply of fat and (2) as a source of protein The protein of soy beans is excellent with respect to all of the essential amino acids except cystine The same, indeed, is true of common beans But since wheat flour contains cystine, the use of beans with bread or better still of baked beans and brown bread provides a source of protein which is adequate The vitamin values of the soy bean compare favorably with those of meat, the choline content is higher than that in leafy vegetable roots and grains In the war soy bean flour that was free of fat found a ready outlet for some purposes, notably in doughnut manufacture Its widespread household use however, lagged far behind what had been desired Milk made from soy beans has proved its usefulness especially for the feeding of children and invalids in regions of the world, especially in China, Thailand and India, where other milk is unavailable A cookbook devoted entirely to the soy bean contains precise directions and a large group of recipes for using both the garden type of soy bean and the flour prepared from field beans

The peanut crop was also much expanded in the war years In this instance consumer acceptance was more satisfactory Sherman has pointed out that beans peas peanuts and soy beans could assume a considerably larger part in the human diet with nutritional as well as agricultural advantage

Wheat germ and corn germ customarily diverted to animal feeding by the millers of flour and degerminated corn meal represent a source of protein of high biologic quality that is of more importance than has been assumed It is estimated that some 150 000 000 pounds (68 038 800 Kg) of wheat germ and 600,000 000 pounds (272 155 000 Kg) of corn germ might be made available for human consumption in this country The total amount has been compared to the 500 000 000 pounds (226 796 000 Kg) of skim milk powder produced in 1941

Another source not only of a protein reputedly excellent in biologic quality but also of fat is the sunflower seed The nutritive value of sunflower seed has long been recognized especially in Russia where great quantities are consumed Sunflower grows in almost any soil and its cultivation might be increased with advantage in many countries

Yeast—An almost limitless potential source of protein of relatively high nutritive value is yeast Mention was made of yeast in our earlier paper, but more information is now available because extensive effort was directed toward its development in the war years Production of yeast for food was undertaken in this country, in Germany, in England in Jamaica and in Puerto Rico Food yeast was grown under primitive conditions and used apparently with great advantage in an internment camp in Java Yeast requires sugar for its growth likewise a source of nitrogen For the latter, ammonia will suffice In the camp in Java a diastase was obtained by growing mold on corn and with this diastase sugar was produced from starch wastes such as old inedible potatoes For the source of nitrogen spoiled fish and spoiled meat were used and when the amounts of these proved insufficient ammonia was distilled from urine The weekly yield of food yeast amounted to more than 60 Kg an amount significant as a supplement to the meager diet provided by the Japanese In Puerto Rico surplus molasses was the culture medium with urea obtained from sewage supplying the nitrogen In Germany, yeast was cultured on wood sugar in amounts said to have exceeded 100,000 tons a year

The protein of yeast has been found to be deficient in the sulfur-containing amino acids methionine and cystine however methionine may not be required by man if his diet contains cystine Cystine is contained in the protein of rice or wheat and either rice or wheat flour usually constitutes a large part of the diets of people obtaining little animal protein Deficiency of yeast in sulfur-containing amino acids, therefore, may not represent a serious disadvantage to the use of yeast The studies in Puerto Rico supported the opinion that the protein of food yeast (Torula) is lower in biologic value and hence lower in net protein value than that of dried brewers yeast and yet as good as that of soy flour and much superior to that of navy beans rolled oats, whole wheat flour and whole corn A purified yeast protein obtained in Germany by treatment of yeast with alkali and subsequent precipitation with acid alcohol was found effective in maintaining nitrogen balance in experiments on man, white rats and hogs

From 24 to 36 per cent of the total nitrogen of yeast is nonprotein nitrogen, a relatively large part of which is present in the form of purines, and the effect of this when yeast is used in human nutrition appears not as yet to have been fully explored Large daily doses (130 Gm) increased the *concentration of uric acid* in the blood and urine On the other hand relatively smaller amounts did not have these effects An amount of yeast as small as 10 Gm daily, to judge from studies made by Sure with rats may be of value as a supplement to the proteins of white flour or white rice It is possible that further experiments will lead to the development of food yeasts which contain less purines Numerous methods have been developed for incorporating yeast in breads soups and other foods The greatest need for food yeast would appear to be *in India in China and in the tropics where population* pressure on the land or economic conditions or both are great enough to make impossible provision of enough meat and milk to supply the population with protein of high biologic quality The cost of yeast is small and addition of it in amounts not more than 3 per cent might help enormously when diets are strictly vegetarian

Cultures of other micro organisms may serve as protein food for man *Fusarium lini* Bolley with a supplement of thiamine provided adequate amounts of the B *complex vitamins for the normal growth reproduction* and lactation of mice Fed to mice as the only source of protein at a 15 per cent protein level, growth was as satisfactory as with 18 per cent of casein The possibilities as foods of this Fusarium and related molds appeared to Vinson and his colleagues to be important, for they can be easily grown in the course of the alcoholic fermentation of the 6 and 5 carbon atom sugars present in wood hydrolysates sulfite waste liquors and silage

FOODS FOR RELIEF

Foods best adapted for stockpiling or for shipping to areas in need of relief must be relatively imperishable and largely free from water In the emergency of any war or major social turmoil transportation at once becomes a problem of immense importance Freight cars and ships in wartime are in great demand for moving troops and military stores and the facilities that can be obtained for moving food are rarely ever

adequate to meet requirements fully Moreover, transportation is peculiarly sensitive to enemy attack In Germany, near the war s end and later in the occupation period, collapse of transportation contributed as much or more to famine as did shortage of the total food supply White flour, white rice degerminated corn sugar and fats and oils best meet requirements for stockpiling and shipping They, however, for the most part are poor providers of minerals, vitamins and the better proteins Among foods best suited to supply these factors are cheese dried beans dried peas and dehydrated (or for certain purposes canned) milk, eggs, meat and fish

Canned food has played a role in every recent war, but never a greater one than in the war just passed Its contribution to maintaining the nutrition both of the military and civilian populations of this country and of our allies was tremendous Canned milk canned meat, canned fish and great varieties of canned vegetables and fruits were shipped to all parts of the world in quantities as large as means of transportation would permit From the standpoint of imperishability and good nutritional quality, foods preserved by modern canning methods rank among the best They also lend themselves to stockpiling Their only disadvantage is that their weight and bulkiness complicate their transportation

Dehydration as a means of saving shipping space represented a major contribution in solving the problem of providing Britain with food enough to keep its people fed in World War II In the years before the war about 3 000 000 tons of water were imported into Britain This was contained in the food that came from overseas Much of that wasted effort was overcome by shipping foods from which the water in large part had been removed Eggs were dried Before the war British imports included 2 000 000 000 eggs of which 75 per cent (or 100 000 tons) was water Fresh meat for transport overseas called for refrigerated ships whereas dried meats could go in any kind of boat Dried soups were shipped in quantity Cheese and butterfat were in great demand as shipping items since they were relatively free of water Powdered eggs was produced and shipped in enormous quantities It proved unsatisfactory until methods were developed which insured good solubility With the better products

which eventually were provided, omelets, cakes and custards could be made which equalled those prepared with fresh eggs However, the most important items in this category were evaporated milk and dried skim milk

Milk—Wherever liquid milk can be obtained it represents a most acceptable and satisfactory means for obtaining protein of high biologic quality Goat s milk possesses about the same nutritive properties as cow s milk, but goats can thrive in rocky country where cows do poorly In such places raising goats for local con sumption of their milk and meat has been encouraged Fluid milk, however, because of bulk and perishability is expensive to transport to distant regions The handi cap is largely overcome by processing before shipment Evaporated milk dried milk and many forms of cheese are relatively imperishable occupy relatively little ship ping space and compared to fluid milk can be delivered to a distant market at a relatively low cost

The nutrients of fluid milk are retained in processing with few exceptions An important exception is the vitamin ascorbic acid which is much reduced It can be restored to evaporated milk after processing but so far this has not become a general practice Its addition to powdered milk is probably impractical Losses as high as 62 per cent occur in the thiamine con tent of evaporated milk but only on protracted storage at room temperature However even fresh milk is normally of little value as a source of thiamine and ascorbic acid Milk is useful mainly for its first class protein its calcium its riboflavin and its vitamin A From the hygienic point of view evaporated milk and dried milk offer the safest possible methods of dis tribution

American production of evaporated milk increased in the war years from about 2 000 000,000 to nearly 4 000 000 000 pounds The product has been extremely valuable for infant feeding so much so that a threatened shortage occasioned by large exports chiefly to our mili tary forces which occurred in 1943 provoked extreme concern in some areas of the United States The prob lem was aggravated because of the insistence on the part of some physicians on the use only of certain widely advertised brands There was no lack of evaporated milk even in the areas where complaints of shortages

were greatest The shortages related to the well known brands The physicians who were responsible for this situation should have known but did not know, that all evaporated milk must now conform to government standards and that one brand cannot be regarded as superior to another

A great deal of evaporated milk is used by adults especially in areas of this country and in other lands where fresh milk is difficult to obtain owing to economic or geographic reasons Although differing in taste from fluid milk its taste is not unpleasant or a handicap to its acceptance Evaporated milk is superior nutritionally to sweetened condensed milk because of the dilution of the latter with sugar which carries calories but no other nutrients Sweetened condensed milk has lost its place in infant feeding where its high content of sugar proved to be a disadvantage Its present use is mainly that of an ingredient of other manufactured foods, bakery goods ice cream candy and the like The amount so used trebled in the war years mainly as a means of evading sugar rationing

More economical than evaporated milk from shipping and other standpoints is milk from which all water has been removed Production of dry milk for human food was doubled by the critical demands of the war and now is said to amount to 1 000 000 000 pounds (453 592 000 Kg) a year representing 10 000 000 000 pounds (4 535 920 000 Kg) of liquid milk Dry whole milk if not too long in storage has no off flavor and tastes like fresh whole milk Dry skim milk its name now changed by Congressional Act to nonfat milk solids' can also be reconstituted to a liquid milk with the taste of fresh skim milk Butterfat or other fat can be added in the process of reconstitution to give a product which resembles fresh whole milk However the more sensible uses of dry milk do not involve reconstitution The dry powder can be directly added to cooked foods of all descriptions A great deal of this product is used by commercial bakers a practice which is highly recommended from the standpoint of nutrition and which also has advantages commercially Bread with added dry milk solids has a more attractive crust and keeps fresh longer Home use of nonfat dry milk solids should be encouraged An extensive use in school lunch programs is anticipated

Dry milk, either dry whole milk or dry skim milk has come to play a part of great importance in feeding undernourished people Its value in the treatment of the famished inmates of Nazi concentration camps was discussed by Pollack It is excellently suited for constructing diets high in protein For this purpose it can be mixed with other foods in large proportions or made into a paste by adding 1 part of dry milk powder to 2 parts of water Whole liquid milk or buttermilk or orange juice may be used as the diluent Flavoring can be added if desired and added egg or powdered egg gives the mixture a custard character with additional nutritional advantages With these products now becoming generally available there is little need for any of the various protein concentrates of fancy composition *appearing in the* drug trade or for the protein hydrolysates which recently have been promoted for oral use There is little evidence that any of these products are absorbed more readily than milk even when digestion is impaired Their cost is out of sight and the atrocious palatability of protein hydrolysates makes them unacceptable even when administered by stomach tube

Among milk products of great usefulness as a source of protein in the war was cheese which rivals any food available as a source of protein is relatively imperishable and lends itself to shipping Very large amounts of American cheddar cheese have been exported and production in this country has increased accordingly American or cheddar cheese has represented about 80 per cent of a total cheese production which now is said to utilize annually about 10 000 000 000 pounds of milk An economic as well as dietary objection to converting milk to cheese is the loss of whey which contains the lactalbumin of the milk some of its mineral and much of its vitamin content Uses for whey have been difficult to develop and to waste this highly nutritious material is well nigh criminal Whey can be dried to powder and used advantageously in bread making much as has been done with dry skim milk It also can be used in candy manufacture but other outlets ought to be explored

FATS AND OILS

A major problem in all the war torn countries and not without real *significance in North America* was the shortage of fats occasioned by the war This

developed from two causes (1) the interruption of imports of coconut, palm and other oils from the Pacific islands and (2) the demand for oil and fat for war use

Fats and oils whether of vegetable or animal origin are edible or inedible depending on their processing None is so rancid but what it can be purified and made acceptable as food In consequence, food uses must compete directly with all other uses especially with production of soap Moreover the process of hydro genation makes possible solidifying oil to any desired degree of hardness and by this means oils from sources such as corn soy beans, rape seed cotton seed or pea nuts can be hardened to the consistency of lard and used as substitutes for lard and butter No great differences exist in the digestibility of fats when the melting point is not above the temperature of the intestine, and the only clearly demonstrated difference in the nutritional value of fats from different sources is in their content of fat soluble vitamins Butterfat contains some vitamin D and is rich in vitamin A and the vitamin A precursor carotene Fish liver oils are the only food sources rich in vitamin D They also contain vitamin A Margarine made either with animal or vegetable fats or oils contains neither vitamin D or vitamin A unless it has been fortified with these vitamins The British required such fortification early in the war years and in the United States almost all margarine is fortified on a voluntary basis to the standard established for fortified margarine by the Food and Drug Administration

The principal plant oils of the United States have been procured from cotton seed linseed soy beans and peanuts The war with Japan stimulated increased planting of soy beans and peanuts which now supply large quantities of oil The recent decline in cotton products and the necessity for raw material to maintain existing oil mills in operation has stimulated a search for new seed oils Sunflower seed castor beans and okra seed are possibilities Okra seed is promising

Insufficient fat in diets leads to much distress The explanation is not entirely apparent Unsaturated fatty acids such as linolic acid are contained in many fats A requirement for them demonstrable in the rat has not as yet been clearly shown for man Although fats serve to increase the digestibility of the provitamin A carotene the distress is not attributed to lack of vitamin A because people living on a largely vegetable diet, as

was necessitated by the conditions existing in Europe in the war, obtain from such a diet large amounts of carotene From the standpoint of providing calories fats and oils are more efficient than any other foods and it is recognized that heavy labor creates a demand for calories which is greater than can be supplied unless a rather large proportion of the needed calories come from fat The stomach of a man engaged in lumbering is simply not large enough to hold an amount of vege tables and cereals sufficient to yield the 5 000 to 7,000 calories which he may require However persons not engaged in heavy labor also complain of fat hunger when fat intakes are lowered to those obtaining in the undernourished population of the European continent Studies by Deuel and his associates may bear on this problem With weanling rats receiving restricted isocaloric amounts of diets varying in fat content growth was greater with diets containing 20 per cent of fat than on similar diets containing only 5 per cent of fat Moreover, mortality from uncertain causes was lower and in a recovery period of ad libitum feeding growth, fertility and lactation were supported better by diets containing liberal amounts of fat Forbes Swift and James found the metabolic efficiency of food utilization to be greater when fat was given

While the evidence for a minimal fat requirement is inconclusive the opinion prevails that 20 to 25 per cent of the total calories should come from fat Half of this total usually should be obtained in a visible form as butter lard and oil The total would amount to from 54 to 68 pounds (24 5 to 30 8 Kg) per year whereas the per capita prewar consumption in the United States was 93 pounds (42 2 Kg) The principal source of invisible fat are dairy products other than but ter, meat nuts and eggs The supply of them as well as the supply of fats and oils has been short in Europe since the war began Much could have been done to alleviate postwar shortage of fat in Europe had the United States adopted a more enlightened program for its use of fats and oils during the war years Because of their relative imperishability fats and oils can be stockpiled over years However such a program involved restriction of the use of fat for soap and for military purposes and resistance was strong enough to prevent any such restrictions

FOOD MANAGEMENT

The successful prosecution of World War II depended to a large extent on the herculean efforts of farmers and other food producers in the United States and Canada Blessed by successive years of better than average growing weather food production was increased almost a third and much of the increase became available for export A further vital contribution involved measures that were introduced for managing distribution, set asides of food commodities price control and differential rationing This is not the place for discussion of food management over the world In due time the story will be told by the Food Research Institute of Stanford University, which has received a large grant of money from the Rockefeller Foundation for a five year study of the subject Some account of procedure in the United States has been given by Hendrickson and by Clayton and Black An account of procedure in Canada has been published under the authority of the Minister of National Health and Welfare The experience of Switzerland has been reported in a recent monograph by Fleisch and separately under the auspices of the Food Research Institute by Rosen

By careful management of their food supplies the Swiss and British came through the war without deterioration and indeed in many respects with actual improvement of the public health Sir William Jameson British Minister of Health, could state in 1946 that infant mortality rates and puerperal death rates had fallen steadily The problem of nutrition in Great Britain received interesting consideration in a recent book by Cruickshank In Switzerland despite lowering of food supplies and shortages of protein and fat the heights and weights of children were maintained The incidence of most reportable infectious diseases was diminished, as was that of diseases of the gastrointestinal tract, including appendicitis

SUMMARY AND CONCLUSION

For populations in the path and in the wake of war finding food becomes a matter of supreme importance By utilizing edibles which in normal times are disregarded, much can be done to alleviate or postpone the worst effects of famine Substantial contributions to the family larder can be made by gardening By these means sufficient vitamins and minerals are usually

obtainable The pressing problems, then, relate to calories and biologically superior protein Cereal grains wheat corn, barley, oats and rye are efficient providers of calories and possess the advantage of being readily transportable However, the proteins of cereals and vegetables fail to provide all the amino acids necessary, moreover a need for fat, which apparently is very real cannot be met with cereals and vegetables alone There fore, planning to meet the food needs of countries over run by war, likewise to meet the needs of areas like India where population pressure excludes the use of land for producing meat and milk, involves attention to supplies of protein and fat Certain resources, espe cially fish can be made to contribute more abundantly Food yeast offers possibilities Yeast and beans soy beans in particular afford proteins which when taken with wheat flour or white rice are reasonably complete Fat production can be augmented by increased plant ing of 'oil seeds such as soy beans peanuts rape and okra and fat can be diverted from other uses in order to increase the amount available for food Foods for distant shipping in conditions of emergency, likewise foods which lend themselves to stockpiling must be low in water content and relatively imperishable White flour white rice sugar and fats and oils best meet such requirements They however for the most part are poor in minerals vitamins and superior proteins Among the foods best suited to supply these factors in emergencies are dehydrated milk, cheese dried eggs and fish

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CHAPTER XXVIII

IMPROVING THE QUALITY OF CHEAP STAPLE FOODS

GEORGE R COWGILL

Discoveries in the science of nutrition over the past several decades have made it possible to state more exactly than ever before the many specific factors that are essential for satisfactory nutrition A brief classification of them would include food energy the protein factor, essential fatty acids, indispensable mineral nutrients and the vitamins An attempt to list individually all the substances required gives a total of more than forty items the exact number depending on whether the claims for the existence of certain factors are to be accepted or not In view of this new knowledge it is obvious that foods can now be evaluated in a manner much more precise and specific than was ever possible before These recent discoveries have also included the isolation and finally synthesis on a commercial scale of many of the vitamins thus making it possible to add these factors to foods Such possibilities have naturally received the attention of both the food industry and students of nutrition and public health On the industrial side it has been necessary to solve many technologic problems Nutritionists clinicians and governmental agencies faced with these possibilities have naturally interested themselves in the formulation of principles to be followed in such addition of special factors to foods amounts to be added and related topics

The application of these new discoveries can of course result in the production of new foods that would doubtless be classified for some time at least as novelties or specialties because of their relatively high cost and only slight use by the mass of the population In con-

trast to this, and much more important for public health and preventive medicine is the application that means definite improvement in the quality of cheap foods that occupy prominent places in the dietary To the extent that these staples, already endowed with a high consumer appeal and acceptance can be nutritionally improved, the chances of incidence of diseases representing dietary shortcomings can be reduced and the cause of public health advanced *This article deals with the latter possibility*

THE GRAINS

Discussions of the foods that figure prominently in various dietaries throughout the world therefore staple foods,[1] are usually in terms of their contribution to the energy needs of the population Cereal grains constitute the cheapest source of food energy in the diets used throughout the world In the United States as a whole the two cheapest sources of calories are cereal products and cane sugar In southern China and certain other parts of the Orient rice is the most economical and readily available food and therefore the most widely used cereal From the standpoint of worldwide use rice comes first this cereal is eaten by more people than any other member of the cereal grain group The dominant cereal used as human food in the United States as a whole is wheat, in certain areas, notably the southern states where pellagra is endemic, corn is eaten in considerable amounts as a staple cereal

The greater keeping qualities of milled cereals in contrast to the whole grain together with the exigencies *of modern civilized life such as ease of transportation* over long distances has resulted in some degree of milling of the grain becoming the established custom a practice which, *from the standpoint of nutritive value* of the material means loss in corresponding degree It is not surprising, therefore that the addition of essential *vitamins and mineral nutrients to milled cereal* products should have received serious attention as one

1 Bennett M K Wheat in National Diets Wheat Studies of the Food Research Institute *Stanford University 18: 37 (Oct) 1941*

of the new possibilities for application of modern nutritional knowledge in the interest of preventive medicine[2]

Interest in this possibility of improving the nutritive value of wheat flour finally resulted in the establishment by the Food and Drug Administration of the federal government of standards for what has been officially designated "enriched" flour[3] The term *enriched* was finally selected as the best one to use in describing products of this sort because it was believed to be least open to undesirable interpretations or misleading implications of one kind or another By its use as part of the name for various products for which official standards of identity have now been established this term has acquired a certain special legal status which is not the case for other words that have figured in much of the discussion of this general subject the word *fortified* for example The first standards for wheat flour, established in 1941, were modified in July, 1943, to include those for enriched white flour The data given in table 1 are based on the 1943 amendments to the original order In 1946 standards for enriched macaroni products and enriched noodle products were established[4] The association of corn eating with a high incidence of pellagra and the importance of the "pellagra problem" in our Southern states stimulated study of the question of enrichment of corn products, and this finally led to the establishment in 1947[5] of standards for enriched corn meals and enriched corn grits These several standards for enrichment are summarized in table 1

Many of the individual states have passed laws requiring the enrichment of white flour and bread—so-called enrichment legislation Twenty-six states and Hawaii and Puerto Rico now have such laws Students of this development will find interesting information in a series of documents issued by the Committee

2 Cowgill, G R The Need for the Addition of Vitamin B_1 to Staple American Foods J A M A. **113**:2146 (Dec.) 1939

3 Definitions and Standards of Identity for Flour and Related Products Federal Register **6**:2574 (May 27) 1941 Wheat Flour and Related Products Amendments to Definitions and Standards of Identity ibid **8**:9115 (July 3) 1943

4 Alimentary Pastes Amendments to Definitions and Standards of Identity Federal Register **11**:7503 (July 6) 1946

5 Corn Flour and Related Products Definitions and Standards of Identity Federal Register **12**:3110 (May 13) 1947

on Cereals of the Food and Nutrition Board National Research Council[6]

The importance of white rice as the staple cereal for people in the Orient has been mentioned "In the United States rice is a staple for only small segments of the population chiefly in certain former and present rice growing areas,'[7] notably Louisiana Arkansas Texas and California, their rice production although it increased by 95 per cent during the decade 1934 1944 has been estimated to be less than 2 per cent of the world production The possibility that milled white rice might be nutritionally improved whether by some process of enrichment or other method has had some attention in the United States The work done on this question up to June 1945 is well summarized in the National Research Council's Bulletin 112[7] It appears that from the technologic point of view it is much more difficult to enrich white rice than wheat flour or corn products nevertheless considerable progress along this line has been made Some large scale trials of white rice that has been nutritionally improved by one of these newly developed processes have been started on certain Oriental population groups[8] to see what effect if any consumption of the new product may have on the hitherto high incidence of beriberi

PRINCIPLES GOVERNING ENRICHMENT OR FORTIFICATION

Discussion of this enrichment or fortification problem has brought out many suggestions of principles and facts to be considered when making additions of vitamins and minerals to foods It is pertinent to inquire whether a lack of the dietary essential in question in the ordinary diet is sufficiently widespread to justify

6 Enrichment of Flour and Bread A History of the Movement National Research Council Bulletin no 110 November 1944 The Facts About Enrichment of Flour and Bread report of Committee on Cereals Food and Nutrition Board National Research Council October 1944 and Supplement March 1946 Bread and Flour Enrichment 1946 1947 report of Committee on Cereals Food and Nutrition Board February 1947 Progress of Bread and Flour Enrichment editorial J A M A 135:226 (Sept 27) 1947 Outlook for Bread and Flour Enrichment Review of Events During 1947 1948 report of Committee on Cereals Food and Nutrition Board November 1948

7 The Nutritional Improvement of White Rice National Research Council Bulletin no 112 June 1945

8 Salcedo J Jr Carrasco, E O Jose F R and Valenzuela R C Studies on Beriberi in an Endemic Sub Tropical Area J Nutrition 36: 561 (Nov) 1948

TABLE 1—*Current Standards for Enrichment and Fortification of Foods**

Federal Standards for Enrichment

Food Enriched	Enrichment Factor								
	Required					Optional			
	Thiamine (Mg per Lb) From	Riboflavin (Mg per Lb) From	Niacin or Niacin amide (Mg per Lb) From	Iron (Mg per Lb) From	Calcium (Mg per Lb), From	Vitamin D (U S P Units per Lb) From	Calcium (Mg per Lb) From	Wheat Germ (Percentage) NMT †	Dried Yeast (Percentage) NMT †
White flour [a]	2.0 to 2.5	1.2 to 1.5	16 to 20	13 to 16.5		250 to 1 000	500 to 625	5	
Self rising flour [b]	2.0 to 2.5	1.2 to 1.5	16 to 20	13 to 16.5	500 to 1 500	250 to 1 000		5	[illegible]
Macaroni and noodle products [c]	4 to 5	1.7 to 2.2	25 to 34	13 to 16.5		250 to 1 000	500 to 625	5	
Corn meals and corn grits [d]	2.0 to 3.0	1.2 to 1.8	16 to 24	13 to 26		250 to 1 000	500 to 750	[illegible]	1.5

Other fortifications of foods Oleomargarine fortified with vitamin A (Federal Register 6 2 01 June 7 1941) not less than 9 000 U S P units of vitamin per pound most oleomargarine is fortified to contain 15 000 units per pound Milk fortified with vitamin D the Council on Foods and Nutrition of the American Medical Association approves milk containing up to 400 U S P units per fluid quart or reconstituted quart Iodized table salt the Council on Foods of the American Medical Association accepts salt containing 0 01 per cent of potassium iodide or equivalent of sodium iodide provided distribution of the iodide in the salt is uniform and the concentration is present after storage under ordinary conditions The Food and Nutrition Board of National Research Council also has approved of this standard

† Signifies not more than by weight of finished product

on Cereals of the Food and Nutrition Board, National Research Council[6]

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7 The Nutritional Improvement of White Rice National Research Council Bulletin no 112 June 1945

8 Salcedo J Jr Carrasco E O Jos F R and Valenzuela R C Studies on Beriberi in an Endemic Sub-Tropical Area, J Nutrition **36**: 561 (Nov) 1948

the existence of malnutrition in our population, Jolliffe, McLester and Sherman[9] believe that such malnutrition is sufficiently widespread to justify taking measures to obviate it The Committee of the Food and Nutrition Board on Diagnosis and Pathology of Nutritional Deficiencies undertook an extensive collection of data bearing on this subject and published in a National Research Council Bulletin its considered judgment of this available information[10] In its summary (page 46) the committee wrote, All the data from numerous surveys with new methods among persons of all ages in many regions are entirely in accord in showing that deficiency states are rife throughout the nation Relatively few are the traditional severe acute types Most are milder in intensity and gradual in their course Predominantly they are subacute or chronic states some marked but many mild or moderate It should be mentioned that not all workers have agreed with this view Further research should no doubt resolve this controversy

VITAMINS AND MINERALS

In 1939 the Council on Foods and Nutrition of the American Medical Association considered this general question of the addition of vitamins and minerals to foods and adopted the following statement[11] as an expression of its policy a statement that has since been reaffirmed[12]

> The Council on Foods desires to encourage the restorative addition of vitamins or minerals or other dietary essentials in such amounts as will raise the content of vitamin or mineral or other dietary essential of general purpose foods to recognized high natural levels with the provision that such additions are to be limited to vitamins or minerals or other dietary essentials *for which a wider distribution is considered by the Council to be in the interest of the public health*

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9 Jolliffe N McLeste J S and Sherman H C The Prevalence of Malnutrition J A M A **118**: 944 (March 21) 1942

10 Inadequate Diets and Nutritional Deficiencies in the United States report of Committee on Diagnosis and Pathology of Nutritional Deficiencies Food and Nutrition Board National Research Council Bulletin no. 109 November 1943

11 Annual Meeting of the Council on Foods J A M A **113** 680 (Aug 19) 1939

12 General Decisions on Foods and Food Advertising report of Council on Foods and Nutrition, July 1946 pp. 51 52

the proposed addition of it to appropriate foods If no real need for such addition can be shown, one may well question the wisdom of it as a socially planned and directed move, its chief justification then becomes a commercial one dependent for its success almost entirely on advertising and other promotional activities of units of the food industry

If there are reasonable grounds for believing that a serious deficiency of the dietary factor of interest does exist, the question arises as to the most suitable food to be enriched or fortified with it There may be rather general agreement as to the class of food to be enriched, but it does not necessarily follow that all products in this class should be so treated As an example, one may consider the fortification of lard with vitamin A Since this animal fat is widely used in cooking and such use results in appreciable loss of the vitamin a conservative attitude toward the question of the addition of vitamin A to lard is justified It is obvious that a body of facts regarding the need for various dietary essentials and the probable supply in common foods is required, as well as information of the technologic sort concerning the feasibility of the proposed addition to any given food product before approval should be given any specific proposal of enrichment or fortification

Concerning this question of need for particular dietary factors by the American people numerous papers may now be cited Students of nutrition have long agreed with Sherman that there is a real likelihood of a significant deficiency of calcium and therefore there is justification for promoting wider use of calcium rich foods like milk milk products and green leafy vegetables There are also reasons for believing that the American diet is not as rich in thiamine as it should be The testimony offered in the hearings held by the Food and Drug Administration which resulted in the federal standards for enriched flour supported the view that the average American dietary does not furnish amounts of some essential vitamins and minerals sufficient to insure the public health so far as these dietary factors are concerned On the basis of the evidence they have summarized concerning

5 That the addition of other than natural levels of vitamins and minerals to foods which are suitable as vehicles of dis tribution may be sanctioned when more natural routes are practically unavailable as ways to correct known nutritional deficiencies

6 That, at present the Committee favors appropriate enrich ment of flour and bread (and perhaps corn meal) the fortifica tion of milk with vitamin D the suitable addition of vitamin A to table fats and of iodine to salt for dietary use. There is no information available to the Committee at the present time which indicates that it is desirable for the Committee to recom mend the addition of vitamins or minerals to foods other than those named

7 That, specifically the Committee opposes the addition of synthetic vitamins to carbonated beverages and confectionery

From the statement quoted it is evident that at the time it was written (1941) the idea of adding vitamins and minerals or other dietary essentials, to foods had been accepted sufficiently to secure official sanction in the following cases the appropriate enrichment of flour and bread (and perhaps other cereal products) with several factors the fortification of milk with vitamin D of table fats with vitamin A and of table salt with iodine Since that time official enrichment standards have been established for the white flour products macaroni and noodles and corn meals and corn grits To what extent other additions will finally acquire widespread acceptance and then official approval only time and the accumulation of new pertinent data can determine

When it has been agreed that certain dietary essentials may well be added to particular foods or classes of foods, the question arises as to how much should be added The discussion of this problem has been most interesting to follow It has been argued that a worth while principle to apply is that of restoration of the milled or processed food by appropriate addition of dietary factors to give a product approximating the natural food source, whole wheat flour for example as contrasted with highly milled white flour This has been called the principle of restoration Paragraph 4 of the statement of the National Research Council Committee is based on this idea of restoration' of the milled product to something comparable to the natural one

In the 1946 reaffirmation of this statement[12] will be found additional sentences, as follows

Addition of vitamins or minerals should be limited to cheap staple foods which occupy substantial places in the dietary

The Council is opposed to the *indiscriminate* fortification of general purpose foods with vitamins or minerals or other dietary essentials By fortification is meant the addition to a food of such an amount of a vitamin or other dietary essential as to make the total content larger than that contained in any natural (unprocessed) food of its class

The words I have italicized are particularly pertinent here, because they state important limitations which not only the Council has adopted when expressing its approval of such additions but the Committee on Food and Nutrition (now Food and Nutrition Board) of the National Research Council

The Committee on Food and Nutrition of the National Research Council expressed its views on this question in the following resolution which has also been reaffirmed since

Whereas There exist deficiencies of vitamins and minerals in the diets of significant segments of the population of the United States which cannot promptly be corrected by public education in the proper choices of foods be it resolved in order to correct and prevent such deficiencies

1 That the Committee endorses the addition of specific nutrients to staple foods (as indicated under 6 below) which are effective vehicles for correcting the above deficiencies in the diets of the general population or of significant advantage of geographic economic or racial segments thereof

2 That the Committee opposes the inclusion or additions of specific nutrients under definitions and standards which may be promulgated under the Food Drug and Cosmetic Act, except in the case of foods which constitute such effective vehicles of distribution

3 That the Committee favors unequivocally the fulfillment of the nutritional needs of the people by the use of natural foods as far as practicable and to that end encourages education in the proper choice of foods and the betterment of processes of food manufacturing and preparation so as to more fully retain the essential nutrients needed thereto

4 That to avoid undue artificiality of food the Committee favors whenever practicable the choice as vehicles for the corrective distribution of vitamins and minerals of those food which have suffered losses in refining processes and recommends that the vitamins and minerals added to such foods should preferably be the kinds and quantities native therein in the unrefined state

stantial parts of the population and are not likely to be available soon nor are most consumers sufficiently educated on nutritional questions to enable them to make an intelligent choice of combinations of unenriched foods on the basis of nutritional values

Because of the lack of adequate production of a number of foods high in certain nutrients and the lack of consumer knowledge of nutrition appropriate enrichment of a few foods widely consumed by the population in general or by significant population groups will contribute substantially to the nutritional welfare of consumers and to meeting their expectations of benefit Enrichment of those foods which are not a substantial part of the dietary of any significant group tends to confuse and mislead consumers through giving rise to conflicting claims of nutritional values and by creating an exaggerated impression of the benefits to be derived from the consumption of such foods

If the customary process of manufacturing a staple food refines it so as to remove significant quantities of nutritive factors present in the natural product from which the food is made and if the refined food is a suitable and efficient carrier of the factors so removed, some nutritionists advocate the restoration of such factors to the levels of the natural product as the most desirable basis of enrichment. To the extent that restoration serves to correct deficiencies of such factors it is consistent with the promotion of honesty and fair dealing that refined foods be enriched on a restoration basis However when the evidence shows that the restoration levels are too low to correct deficiencies or that deficiencies exist in other factors for which the refined food is an efficient carrier the promotion of honesty and fair dealing may require the inclusion of corrective quantities of nutritive factors in the enriched food even though such factors are present in smaller quantities or wholly lacking in the natural product from which the food is made Similar considerations may require the enrichment of unrefined foods.

When a single dietary factor is being considered this principle has much to commend it For example the processing of a fruit juice may result in appreciable loss of vitamin C, and products of this sort are normally valuable as sources of this factor An obvious procedure of great value here is improvement in the methods of processing so as to reduce such losses to a minimum Such a juice could also be restored to approximately the highest concentration characteristic of the natural juice by the addition of ascorbic acid The principle of restoration proves to be unsatisfactory however, when the addition of more than one factor is being considered In the case of ordinary wheat

The following statement of the policy of the federal government with respect to the addition of nutritive ingredients to foods,[13] is of interest in this connection

The labeling or advertising of a food as enriched with vitamins and minerals is an implied promise to consumers that it contains in addition to the normal constituents of the unenriched food, sufficient vitamins and minerals to make substantial contribution to the nutritional welfare of persons eating the enriched food in customary amounts In order to promote honesty and fair dealing by fulfilling this implied promise it is necessary that the kinds and quantities of enriching ingredients be determined in the light of deficiencies of the various nutritional factors in the diets of the population in general and of significant population groups the place occupied by the food in such diets and the suitability and effectiveness of the food as a carrier of the enriching ingredients without undue separation or loss before consumption

Honesty and fair dealing will best be promoted if such enriched foods as are made available to consumers serve to correct such deficiencies and furnish a reasonable margin of safety Enrichment above the levels required to accomplish this end is wasteful and contrary to the interest of most consumers nutrient factors in concentrated form are available for use in those special cases of deficiencies in the diets of persons who do not constitute significant population groups. Enrichment of foods with nutrients that are supplied in adequate quantities by the diets of all significant population groups is not only wasteful but tends to confuse consumers as to their nutritional needs

Knowledge of the roles in human nutrition of various components of food particularly the vitamins is incomplete. There is reason to believe that as new information is developed food factors not now recognized as essential may be shown to be necessary to adequate nutrition.

Most natural foods contain a wide variety of needed factors in significant amounts It is highly probable that a diet of unenriched foods so chosen as to contain the required quantities of the presently known needed vitamins and other factors would more nearly supply all needed factors known and unknown, than a diet which is raised by enrichment to adequacy in the vitamins and minerals now known to be needed

Even though adequate nutrition could be better assured through the choice of natural foods than through reliance on enrichment, unenriched foods of the kinds and in the quantities necessary for adequate nutrition are not now available to sub

13 Federal Security Agency Food and Drug Administration. Statement of Policy with Respect to the Addition of Nutritive Ingredients to Foods, Federal Register 8 9170 (July 3) 1943

covering the method was issued and this in turn was given to the Canadian government These developments have culminated in the establishment in Canada of a standardized apple juice which must contain 35 mg of ascorbic acid per 100 ml of juice This might be regarded as an illustration of the point made in the last sentence of the statement of governmental policy cited 'Similar considerations may require the enrichment of unrefined foods'

When several dietary factors are being added to a given staple food, some in accordance with the principle of restoration others in accordance with fortification, one is not limiting oneself to making the staple processed food as nearly as possible like the natural source but frankly modifying it to make an entirely new product to meet a particular nutritive situation Enriched flour is the prime example of this In such a case it is evident that the proposed addition of several factors is best made in some relation to the human requirement for them taking into account the other sources of supply available in the dietary and other pertinent considerations It may be questioned whether there are many *staple* foods that would be suitable as vehicles for the wider distribution and intake of several dietary factors instead of only one or perhaps two In view of this there may still be a place for operation of the principle of restoration in the improvement of numerous processed foods

OTHER METHODS OF IMPROVING FOODS

The foregoing discussion has dealt with the ideas that have been advanced for improving staple foods by what might be called the artificial addition of dietary factors lost as a part of food processing There are other ways of achieving the same objective One may select plant varieties on the basis of genetic constitution and vitamin content. It is known that varieties of wheat and other cereals differ considerably in their respective contents of thiamine Data bearing on this topic have been summarized by Taylor [14] and are shown in table 2 In addition to illustrating the variation in thiamine content characteristic of cereal grains

14 Taylor A E. Why Enrichment of Flour? Wheat Studies of the Food Research Institute Stanford University 18:77 (Nov) 1941 (See particularly page 92)

flour, for example, the addition of vitamin B_1 in amount sufficient to make the flour approximately equal to whole wheat with the highest natural concentration means a significant addition of the restorative sort a restorative addition of riboflavin (vitamin B_2) to the flour, however means little because the cereal grains are not good natural sources of this factor If, therefore, riboflavin is to be added to the flour in significant amounts, the addition means "fortification" because the enriched product will contain even more riboflavin than is found in the natural whole grain It will be noticed in the statement of governmental policy quoted (last paragraph), that this point is discussed

In certain situations where "restoration is proposed, the question is raised as to what food is to be taken as representing a "high natural level' for foods of that class Good orange juice will contain over 40 mg of ascorbic acid per 100 ml of juice, whereas natural tomato juice may contain anywhere from about 3 mg to 33 mg per 100 ml If one is considering how much vitamin C to add to make a restored or fortified product, should the highest levels of the natural juice namely about 33 mg per 100 ml be the reference standard, or should the even higher values characteristic of orange juice be the standard?

Linked with this question is another one relating to fruit juices What should be our attitude toward a proposal to fortify with ascorbic acid a product like apple juice which contains relatively smaller amounts of this factor than citrus and tomato juices? The answer to this question can be very important in certain situations and less so in others Canadian authorities decided that the supply of ascorbic acid in Canadian dietaries is not as high as it should be in order to insure the public health so far as this factor is concerned They reached the conclusion that the people in their country should not be forced to rely for their main supply of vitamin C on imported citrus fruits which have been shipped long distances and therefore are relatively expensive Apples constitute an important crop in Canada Why not develop a standardized C-fortified apple juice for Canada? Fortification of this particular fruit juice with ascorbic acid was found to be technologically feasible a patent

TABLE 3—*Nutritional Improvement of Plant Foods by Experiments in Genetics, Illustrated by Studies on Corn (Maize)*

PROTEIN FAT FIBER AND ASH *

No significant differences in chemical composition of more than 40 commercial hybrids and open pollinated varieties of dent corn

AMINO ACIDS †

"The amounts of certain amino acids in corn proteins are affected, to some extent at least, by the genetic constitution of the plant"

NIACIN

	Number of Strains	Average Mg / 100 Gm	Range Mg / 100 Gm
Burkholder McVeigh and Moyer ‡			
Sweet corn	45	3 46	1.8-6.21
Yellow field	94	2 14	1 13-3.63
White field	86	2 01	1.27-2 94
Popcorn	7	1 74	0 79-2 18

Richey and Dawson §

White dent (24 inbreds) 1.39 to 5.33 mg per 100 Gm
It is concluded that corn hybrids with niacin concentrations as high as 50 micrograms per gram could be developed.

CAROTENE

Hauge and Trost ‖

"The vitamin A content of dent corn is controlled by ordinary hereditary factors These genes are the same as those governing development of the yellow endosperm.

Mangelsdorf and Fraps ¶

Vitamin A content of 4 samples of known genetic constitution were 750 500 25 and 5 units of the provitamin per 100 Gm, respectively

Scott and Belkengren #

Sweet corn 22 inbred lines 0 061 to 0 77 mg per 100 Gm
45 hybrids 0 16 to 0 46 mg per 100 Gm

Porter Strong Brink and Neal **

Entire plant for use as silage carotene content of leaf blades 20 to 50 times higher than rest of plant Total carotene content relatively constant until near end of season then falls sharply Significant differences between stocks both inbred and hybrids exist but are relatively small Sun red gene has no influence.

VITAMIN C

Sweet corn # 22 inbred lines 10 4 to 17 mg per 100 Gm
45 hybrids 9 9 to 18 mg per 100 Gm

* Doty D M Bergdoll M S and Miles S R The Chemical Composition of Commercial Hybrid and Open Pollinated Varieties of Dent Corn and Its Relation to Soil Season and Degree of Maturity A Preliminary Report Cereal Chem 20:115 (Jan) 1943

† Doty D M Bergdoll M S Nash H A and Brunson A M Amino Acids in Corn Grain from Several Single Cross Hybrids Cereal Chem 23 199 (March) 1946

‡ Burkholder P R McVeigh I and Moyer D Niacin in Maize Yale J Biol. & Med 16:659 (July) 1944

§ Richey F D and Dawson R F A Survey of Possibilities and Methods of Breeding High Niacin Corn (Maize) Plant Physiol 23:238, 1948

‖ Hauge S M and Trost J F An Inheritance Study of the Distribution of Vitamin A in Maize III Vitamin A Content in Relation to Yellow Endosperm J Biol Chem 86:167 (March) 1930

¶ Mangelsdorf P C and Fraps G S A Direct Quantitative Relationship between Vitamin A in Corn and the Number of Genes for Yellow Pigmentation Science 73:241 1931

Scott G O and Belkengren R O Importance of Breeding Peas and Corn for Nutritional Quality Food Research 9:371 (Sept Oct) 1944

** Porter J W Strong F M Brink R A and Neal N J Carotene Content of the Corn Plant J Agric Research 72:169 (March 1) 1946.

the data in table 2 emphasize a point frequently forgotten by those who argue that enrichment of flour is unnecessary that the use of whole grain flour is the answer to the basic problem being attacked There is no such thing as a standard whole wheat flour with respect to 'high natural level" of thiamine content The adoption and wide use of a standardized enriched flour in contrast to a *nondescript unstandardized whole* wheat product has therefore some definite points in its favor

A good general idea of what has been done in an attempt to increase the nutritive value of plant foods by genetic experiments can be gained from the data

TABLE 2.—*Thiamine Content of Cereal Grains and Types of Wheat*

Kind of Grain	Thiamine		Type of Wheat	Thiamine	
	Mg /Lb *	Mg / 100 Gm.		Mg /Lb	Mg / 100 Gm.
Oats	2 20-4 90	0 48-1 08	Durum	2 10-3.80	0 46-0.84
Wheat	1 45-3 80	0 32-0 84	Hard spring	1 45-3 49	0.32-0 77
Barley	2 58-3 33	0 57-0 73	Hard winter	1 68-2 71	0 37-0 60
Corn	1.85-3 04	0 41-0 67	Pacific	1 76-2 44	0 39-0 42
Rye	1.88-2.28	0 41-0 50	Soft red	1 79-?.38	0.39-0 52

Original data from Taylor[14] who commented as follows 'The e include analyses of pure varieties and nondescripts (more than random samples) commercial grades and ungraded from good and poor crops *stored for short and longer periods with different methods of assay* The significant spreads cannot be as wide as those given

assembled in table 3 relating to corn Examination of this table will reveal that whereas the contents of protein fat fiber and ash are only slightly, if at all, *affected by genetic constitution*, the opposite is true with respect to contents of niacin, carotene and vitamin C Some idea of the significance of the *figures given for niacin can be gained from con*sideration of the statement made in the paper by Burkholder, McVeigh and Moyer[15] "It would be distinctly helpful if a natural whole corn product containing at least 35 micrograms of niacin per gram could be produced in the South Our studies show that the niacin content of some strains of field corn attain this desired level while a number of sweet corn strains

15 Burkholder P R McVeigh I and Moyer D *Niacin in Maize* Yale J Biol & Med **16**: 659 (July) 1944

constitution[21] in relation to the ascorbic acid content of this vegetable Walker and associates[22] showed that it was possible by selection to secure genetic lines in which the vitamin C content was much higher than that of the parent stock 'The high ascorbic acid character was apparently well fixed and resulted in intermediate levels in the F_1 from crosses with low acid lines That fairly high ascorbic acid content can be combined with high yield, satisfactory type and increased resistance has already been indicated" The following significant statement is made We may expect therefore, to see the development and adoption of cabbage varieties greatly improved in nutritive value, disease resistance, and productivity'[22a]

The sweet potato has been studied with the view to developing varieties of higher nutritional value They illustrate how different varieties of the sweet potato can vary with respect to content of carotene and ascorbic acid In a personal communication Professor Elmer said, "Our method (of study) here in Kansas is through mutation In the South Dr Julian Miller of the Louisiana Agricultural Experiment Station has varieties even higher in carotene content which are the result of genetic crosses I am quite sure that varieties with even higher carotene content will be obtained One of the important results of higher carotene content is that the sweet potatoes become more palatable and I am convinced that these better sweet potatoes of the present time are not only more valuable nutritionally but that they also have more appeal when eaten '[23]

Some staple foods of plant origin can be nutritively improved by the adoption of special methods of cultivation At present we do not know all that we should like to know about the effects of various environmental factors on the vitamin and mineral content of important plants that we use as food The subject is being

21 (*a*) Poole C F Grimball, P C and Kanapaux M S Factors Affecting the Ascorbic Acid Content of Cabbage Lines J Agric Research 68:325 1944 (*b*) Janes [b] (*c*) Walker J C and Foster R E The Inheritance of Ascorbic Acid Content in Cabbage Am J Botany 33 758 (Nov) 1946

22 (*a*) Smith F G and Walker J C. Relation of Environmental and Hereditary Factors to Ascorbic Acid in Cabbage Am J Botany 33 (No 2): 120-129 (February) 1946 (*b*) Walker and Foster[21]

23 Elmer O H Kansas State College, Manhattan Kan., Personal communication to the author

range up to more than 60 micrograms per gram" It is the conclusion of Richey and Dawson [16] authors of the most recently published paper cited, that 'corn hybrids with niacin concentrations as high as 50 micrograms per gram could be developed"

The study by Porter and associates [17] is a little different from the others cited in table 3 in that it relates to the entire corn plant and its value for making silage for cattle Its results constitute a contribution to the question of how to increase the carotene content of silage fed to dairy cattle and thus to affect the vitamin A potency of cow s milk

Progress in this field of research must necessarily be slow because of the fact that the experimenter usually gets only one crop per year and generally seven or eight years are required for purification and standardization of any new hybrid Another factor of importance here relates to other non nutritive characteristics of the plant food such as texture and resistance to disease that determine its commercial processing value Some hybrids may be more valuable from the nutritive standpoint but inferior for one or more non nutritive reasons In such cases considerable further work is obviously necessary in order finally to secure hybrids that have the most desirable combinations of all factors nutritive and non nutritive The interested reader will find an excellent over all account of the problems and developments in this field in the summary article by Garber [18]

Cabbage is one of the economical natural sources of ascorbic acid in the American diet Several investigators have studied the roles of variety [19] season [19] soil fertility [19] locality [20] state of maturity [20a] and genetic

16 Richey F D and Dawson R F A Survey of Possibilities and Methods of Breeding High Niacin Corn (Maize) Plant Physiol **23** 238 1948

17 Porter J W Strong F M Brink R A and Neal N P Carotene Content of the Corn Plant J Agric Research **7**_ 169 (March 1) 1946

18 Garber R J Plant Breeding in Relation to Human Nutrition Science **101** 288 (March 23) 1945

19 (*a*) Burrell R C Brown H D and Ebright V P Ascorbic Acid Content of Cabbage as Influenced by Variety Season and Soil Fertility Food Research **5** ?47 (May June) 1940 (*b*) Janes B F The Relative Effect of Variety and Environment in Determining the Variations of Per Cent Dry Weight Ascorbic Acid, and Carotene Content of Cabbage and Beans Am Soc Horticul Sc **4**_ 387 1944

20 (*a*) Murph E. The Ascorbic Acid Content of Different Varieties of Maine-Grown Tomatoes and Cabbages as Influenced by Locality Season and Stage of Maturity J Agric Research **64** 483 1942 (*b*) Janes [1]

addition to the milk of the vitamin, or a concentrate of it, with such products differing merely in the material added, such a milk is obviously a fortified one Vitamin D may also be added to the milk through the metabolism of the cow by feeding a product like irradiated yeast, which contains the vitamin, or even the vitamin itself This amounts to affecting the environment in which the milk is produced

The addition of vitamin A to milk or its fat derivative butter has received some attention The vitamin A

TABLE 4—*Carotene Ascorbic Acid and Carbohydrate Content of Sweet Potatoes (Moisture Free Basis)**

Variety	1944 Carotene, Mg / 100 Gm	1944 Ascorbic Acid, Mg / 100 Gm.	1946 Carotene Mg / 100 Gm	1946 Ascorbic Acid Mg / 100 Gm	1946 Total Sugars %	1946 Starch %
Nancy group (yam)						
Nancy Hall.	9.2	24.8	3.3	47 0		
Nancy Gold	23.3	25.8	23 5	45 2		
Red Nancy			31 6	72 5		
Jersey group (dry cooking)						
Common Little Stem Jersey	2.9	22.9	3.2	34 7	28.07	43 45
Orange Little Stem No 35	16.9	41.5	36 0	2 4	32.97	33.32
Orlis	41 0		43 1	37 0		
Rols			13 8	1 1		
Orange Little Stem StnP35			36 0	25 4	60.39	15.87

Data obtained through Prof O H Elmer Kansas State College Manhattan Kan

content of butter is known to vary with the season being low in winter and high in summer[28] The development of a butter more uniform in vitamin A content is a worthy objective of the butter industry that has apparently had less attention than it deserves, such a product would be the logical one with which to meet the competition offered by vitaminized oleomargarine Vitamin A concentrates could of course be added to winter butter The experiments of Deuel and his

28 Dornbush A C. Peterson, W H and Olson F R The Carotene and Vitamin A Content of Market Milks J A M A. 114 1748 (May 4) 1940

actively investigated Exposure to sunlight,[24] character of the soil,[25] supply of special materials to the soil,[19a] water supply[26] and similar factors require investigation and have been receiving attention It is an interesting fact that an exceedingly important environmental factor determining the amount of ascorbic acid *present in the tomato* is the amount of exposure of the fruit to sunlight shortly before harvesting[24] A food like the potato which remains in the soil until harvested is known to reflect in its iodine content the iodine concentration of the soil and water[27] In an iodine survey of various sections of South Carolina the iodine content of potatoes grown in the respective areas proved to be as good a criterion of iodine supply as analyses of water and soil In dealing with a shortage of dietary iodine, obviously, then one has several possibilities (*a*) wider use of sea food which is an excellent natural source of this element, (*b*) wide use of a root vegetable like the potato cultivated in an iodine *enriched soil or water or* (*c*) *the fortification with* iodine of a product such as table salt The first two of these possibilities are impracticable for an inland area for obvious reasons but are valuable procedures for coastal regions the problem of inland areas is more easily met by the use of iodized table salt

Nutritive improvement of foods of animal origin like milk and its derivatives can be achieved in accordance with much the same principles Milk is such a valuable food that nutritive improvement of it has not had extensive consideration Most of the discussion of this topic has centered around the use of fortified milk as a means of increasing the supply of vitamin D to growing children and thus improving the utilization of its calcium Vitamin D milk may be obtained by direct

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24 Somers C F Mamner K. C and Nelson W L Field Illumination and Commercial Handling as Factors in Determining the Ascorbic Acid Content of Tomatoes Received at the Cannery J Nutrition **30**:425 1945

25 McElroy L W Kastelic J and McCalla A G Thiamine and Riboflavin Content of Wheat Barley and Oats Grown in *Different Soil* Zones in Alberta Canad. J Research **26** 191 (April) 1948 McElroy L W and Simonson H The Niacin Content of Wheat Barley and Oats Grown in Different Soil Zones in Alberta, Canad J Research **26** 201 (April) *1948*

26. Paull A E and Anderson J A The Effects of Amount and *Distribution* of Rainfall on the Protein Content of Western Canadian Wheat Canad J Research **20** 212 1942

27 *Hayne J A* Endemic Goiter and Its Relation to Iodine Content of Food, Am. J Pub Health **19** 1111 (Oct.) 1929

by voluntary means the enrichment of all its staple flour by every unit of the industry The enactment of laws to solve problems always poses some additional problems of effective enforcement and the like, whether a law will be readily accepted no matter how desirable it may be from a strictly scientific point of view, depends on a sufficiently large portion of the people being properly informed and convinced of its value Thus we are brought around once more to the fact that the fundamental solution of our basic problem lies in effective education of the general public with respect to the principles of nutrition, food values and related topics Given the proper education in these matters the general public will naturally prefer more and more the improved staple foods over those that are not improved, the extent to which this occurs will largely determine the role that this particular application of modern knowledge in nutrition plays in promoting the public health

associates[29] presented the possibility of significantly enriching cow's milk with vitamin A by feeding certain extremely concentrated preparations of the vitamin, studies of this possibility indicate however, that the metabolic transfer of vitamin A through the mammary gland is not economical Improved feeding of cows during the winter season constitutes another approach to solution of this problem The study by Porter and associates,[17] dealing with the carotene content of the entire corn plant in an effort to find a silage richer in carotene for feeding the cow, is an illustration of this approach

From this brief discussion it should be evident that by improving the quality of cheap staple foods it is possible to affect the public health in many important ways The success which attends this method will obviously depend on several factors One is the extent to which the consumer is made aware of the values of the improved product when it is in the market competing with the older unimproved but accepted food The solution of this problem lies in consumer education and in this work the physician can do much because of his influential position in the community If the improved product can be given a favored status of some sort, its use will of course be increased Twenty-six states and Hawaii and Puerto Rico have passed laws requiring all white flour sold in their respective domains to be of the enriched variety and enriched corn meals and corn grits are now available for combating pellagra Louisiana has also passed a law requiring that all oleomargarine offered for sale contain vitamin A This way of achieving greater consumption of a desired product has certain shortcomings as well as advantages In the case of enriched flour used in these Southern states the advantages are evidently believed greatly to outweigh the disadvantages It is especially important that the enriched flour be used extensively by the lower income groups of the population who have the least money to pay for the improved product Unfortunately the enriched flour has not generally proved to be the cheapest It is to the credit of the milling industry that it has sought to bring about

29 Deuel H J Jr, Halliday N Hallman L F Johnston C and Miller A J The Production of High Vitamin A Milk by Diet J Nutrition 22 303 (Sept) 1941

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a rumen fistula) reached the blood[77b] Orally administered labeled cobalt was 80 per cent eliminated in the feces 0 5 per cent in urine[77c] Relatively insignificant absorption was indicated by failure to find cobalt in blood milk or saliva Labeled cobalt injected intravenously in dogs did not appear in significant amounts in the pancreatic juice, but a total of 2 0 to 5 0 per cent was eliminated in forty eight and seventy two hours respectively in the bile[77d]

Cobaltous acetate (500 mg daily) in rations of dairy cows increased the cobalt in milk from 0 6 mg up to 2 4 mg[77e] Comar and Davis[78] compared the distribution of injected radioactive cobalt in swine, rabbits and young calves and found no evidence of species differences Their findings 'support the view that the major function of cobalt in the ruminant is a localized action in the rumen, but do not exclude the possibility of a hematopoietic function'

The foregoing evidence which implicates the liver as an important depository for radiocobalt, is in agreement with the analytic data of Askew and Watson,[79] which showed that radioinactive cobalt given to deficient sheep accumulated in greatest amount in the liver, with only slight increases in spleen and kidney

Cobalt Polycythemia —An exhaustive review of dietary factors (vitamins amino acids and minerals) which are concerned in erythropoiesis has appeared recently[80] Among the minerals involved—iron copper and cobalt —cobalt is unique, i e a deficiency of cobalt results in anemia small amounts of cobalt produce erythropoiesis and larger amounts depress erythropoiesis Although symptoms of endemic cobalt diseases are not specific, involvement of the erythropoiesis is indicated by the anemia which is generally observed in cobalt-deficient animals

Cobalt polycythemia is easily produced in a number of animal species[79] but the mechanism is still unknown A number of reports on this subject have appeared

78 Comar C L and Davis G K Cobalt Metabolism Studies IV Tissue Distribution of Radioactive Cobalt Administered to Rabbits Swine and Young Calves J Biol Chem **170** 379 1947

79 Askew, H O and Watson J Correlation of Cobalt Content of Organs of Healthy and Bush Sick Sheep at Glenhope New Zealand New Zealand J Sc & Tech **25** 81 1943

80 Cartwright G E Dietary Factors Concerned in Erythropoiesis Blood **2**: 111 and 256 1947

recently[81] Wintrobe[81g] studied the effect of cobalt on the anemia produced by inflammation induced by injection of turpentine and found it was largely overcome in the rat by cobalt Cobalt polycythemia was developed in rats regardless of the addition of choline or methionine to the diet but the addition of cystine was distinctly inhibitory[81f]

A role of cobalt in cell metabolism is suggested by its activating effect on arginase[8] Cobalt is also an effective inhibitor of growth and respiration of various micro organisms animal tissues and tumors The action of histidine in overcoming this cobalt inhibitory effect is being studied[83]

ZINC

A comprehensive review of zinc emphasizing its toxicity has been presented[84] Prior to this survey[84] it was surmised that use of zinc in war production might have produced unsuspected features of zinc toxicity No new toxic manifestations were noted however and the usual precautions in industrial production and use of zinc are still necessary

Interest in a requirement of zinc is stimulated by evidence of the presence of zinc in purified carbonic

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81 (a) Dorrance S S Thorn G W Clinton M Edmonds H W and Farber S Effect of Cobalt on Work Performance Under Conditions of Anoxia Am J Physiol **139** 399 1943 (b) Davis J E The Effect of Oxygen, Soybean Lecithin Carbamyl Choline and Furfuryl Trimethyl Ammonium Iodide on Experimental Polycythemia J Pharmacol & Exper Therap **79**:37 1943 (c) Warren C O Schubmehl, Q D and Wood I R Studies on the Mechanism of Cobalt Polycythemia Am J Physiol **142**:173 1944 (d) Orten J M and Orten A. U The Production of Polycythemia by Cobalt in Rats Made Anemic by a Diet Low in Protein Am J Physiol **144**:464 1945 (e) Stanley A J Hopps H C. and Hellbaum A A Observations on Cobalt Polycythemia I Studies on the Peripheral Blood of Rats Proc Soc Exper Biol & Med **61** 130 1946 (f) Bucciero M C and Orten J M The Effects of Certain Amino Acids and Choline on the Production of Polycythemia by Cobalt, Federation Proc **6** 403 1947 (g) Wintrobe M M Grinstein M Dubash J J Humphreys S R Ashenbrucker H and Worth W The Anemia of Infection VI The Influence of Cobalt on the Anemia Associated with Inflammation, Blood **2**:323 1947

82 Sumner J B and Somers G F Chemistry and Methods of Enzymes ed 2 New York Academic Press Inc 1947 Anderson A B Activation of Jack Bean Arginase by Cobalt Manganese and Iron Biochem J **39**:139 1945

83 Burk D Hearon J Caroline L. and Schade A L. Reversible Complexes of Cobalt, Histidine and Oxygen Gas J Biol Chem **165**:723 1946

84 Hegsted D M McKibbin J M and Drinker C K. The Biological, Hygienic and Medical Properties of Zinc and Zinc Compounds Supplement 179 to the Public Health Reports, Federal Security Agency United States Public Health Service 1945